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THE EPIDEMIOLOGY OF ACUTE RESPIRATORY INFECTIONS CONDITIONED BY SULFONAMIDES. I. GENERAL CLINICAL CONSIDERATIONS *

By MORRIS SIEGEL and L. A. JULIANELLE,† *New York, N. Y.*

ALTHOUGH an impressive proportion of public health problems associated with prevention of disease has been solved in a gratifying manner, it must be admitted that in the case of respiratory infections as a class prophylaxis remains to be accomplished. Withstanding the attempts made in the past with prophylactic immunization, spraying preparations, personal hygiene, isolation, and, to a limited extent, ultraviolet radiation and aerosols, the still resistant examples of this group of diseases apparently must be controlled by newer methods of approach. It was reflected in this connection that by virtue of their bacteriostatic action, sulfonamides might be of value in certain instances in attaining the desired objective. Even in instances of virus infection (e.g., common cold, influenza, atypical pneumonia) it was reasoned that benefit might be achieved because of the retarding influence of the drugs on the growth of those organisms most commonly implicated in secondary complications, even though the primary or viral agent is itself unaffected. That such predication might actually be the case was indicated by preliminary studies already published from this laboratory.[1, 2] Thus, it was revealed that prompt prescription of sulfadiazine at the onset of acute symptoms of the upper air passages was followed in certain cases by a decrease in the severity and duration of complications. Favorable clinical effects attributable to sulfadiazine were ascribed to the inhibitory behavior of the drug on susceptible, offending organisms.

During the fall and winter of 1942–1943, a more elaborate study was undertaken of the value of sulfadiazine in the control of the more common

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acute respiratory infections. The investigation was conducted over an extended period in a closed population at Letchworth Village,[3] a state (New York) institution for the feebleminded. Both clinical and bacteriological observations were made, but in the present communication only the former will be reported.

Method of Study

1. Subjects under study. The individuals utilized in the survey were inmates of a single cottage (Iota) in the institution. The cottage accommodated 130 children of the lowest mental rating, who by past experience proved to be particularly susceptible to both acute respiratory infection and secondary bacterial complications. The ages varied from two to 15 years, with the average about eight years. Some 25 of the youngest subjects were housed in a nursery, while the remainder slept in two dormitories containing 50 to 60 beds spaced only several inches apart and arranged in three rows at intervals of about three feet. Excluding those in the nursery, the children were allowed to intermingle in the cottage without restriction so that contact was close and intimate. Their activity was limited and consisted almost entirely of sitting or aimless wandering within the confines of the cottage and an adjoining outdoor porch. Although association with the inmates of other cottages was confined entirely to necessary visits to clinic or hospital, contact with individuals other than those residing in Iota cottage came through employees, inmate-workers, visitors (usually on Sundays and holidays), and new admissions who replaced withdrawals at the average rate of one or two a week. Of the 130 children, 60 were selected for study. In alternate order of admission, 30 were allocated to a group receiving sulfadiazine ("treated group") and 30, to a control or "untreated" group.

About 88 per cent of the children in the study were white and 12 per cent colored. The duration of residence at the institution varied from three months to seven years; about 53 per cent had been in the cottage for two or more years, 27 per cent for one year, and 20 per cent for less than a year. Their ages varied from four to 14 years, the average being 7.5 years for the treated and 7.7 years for the controls. Their weights ranged from 32 to 88 pounds, with about 55 per cent fluctuating between 40 and 60 pounds. The average weights were 46.8 pounds for the treated and 48.7 pounds for the controls. The frequency of mongolism was high, attaining a rate of about 23 per cent.

Comparative data on the number of acute respiratory infections observed in the two groups during the year preceding the study are summarized below. The infections listed occurred entirely during the period of the previous year corresponding to that of the present year's study. During 1941–1942, the year preceding the test period, 100 colds were observed among the children in the study, 49 in the treated group and 51 among the controls. During the same interval, three of the children in each group had lobar pneu-

Colds per child during year preceding test period (Dec. 1941–Mar. 1942)	Treated group		Control group	
	Children	Colds	Children	Colds
0	9	0	11	0
1	7	7	8	8
2	6	12	1	2
3	5	15	4	12
4	1	4	2	8
5	1	5	3	15
6	1	6	1	6
Total	30	49	30	51

monia due presumably to Pneumococcus types I, V, VI, VII, XIV, and XXII.

The foregoing data reveal that the two groups selected for study were similar in respect to physical development, mental characteristics, duration of residence at the institution, and incidence of endemic respiratory infections including pneumonia.

2. Administration of drug. Sulfadiazine * was used daily in the treated group from December 11, 1942 to March 25, 1943, a period of 15 weeks ("test period" or "period of drug therapy"). During the first two months (December 11 to February 10) one gram (2 tablets) of the drug was given daily in three divided doses as follows: 0.25 gram (½ tablet) at 6 a.m. with breakfast, 0.25 gram (½ tablet) at 11 a.m. with lunch, and 0.5 gram (1 tablet) at 6 p.m. with an egg-nog. After February 10, the daily dosage was doubled to two grams, given in four equally divided portions of 0.50 gram (1 tablet) at 6 a.m. with breakfast, 11 a.m. with lunch, 4 p.m. with dinner, and 8 p.m. with an egg-nog. This method of administration was maintained for a period of six weeks, from February 11 to March 25. Within the entire period of daily drug therapy, then, each treated child received a total of 148 grams of sulfadiazine. After March 25, the drug was used only in the event of acute respiratory infection, and then for seven days: two grams daily for the first four days and one gram daily for the last three days. Only those in the treated group received sulfadiazine; except for the use of the drug, the controls were managed as were the treated children.

During the period of drug therapy, all the children were ambulatory and permitted their usual activities within the cottage. When ill, they were confined to bed within their dormitory and treated in the routine manner, which called for an enema on the first day, a light diet and increased amounts of fluids during the acute stage, and acetylsalicylic acid if needed. In addition, the treated children received sulfadiazine in minimum doses of two grams daily for the first four days of illness and after that, the usual daily dose prescribed in the study. Those who developed pneumonia or became very ill for any reason were transferred to the hospital maintained at the institution.

* The sulfadiazine was supplied by Lederle Laboratories, Inc., Pearl River, New York.

There they were treated in an open ward of 50 beds for one or more days until they were considered well enough to return to the cottage.

3. Collateral laboratory examinations. During the period of daily drug therapy, nasopharyngeal cultures were made every seven to 10 days during the period of daily drug therapy, and every 10 days from May 6 to June 14 in the post-therapy period. The details of the methods employed will be described in reports dealing with the bacteriological data.

Periodic examinations of the blood and urine were also conducted. Red and white blood cell counts (total and differential) were done at weekly intervals, and hemoglobin was determined at monthly intervals. Analyses for non-protein nitrogen were performed on three occasions during the course of the study. Blood specimens for the determination of free sulfadiazine were obtained every seven to 10 days,* at the same time that throat smears were made.

Results Following Administration of Sulfadiazine

Effect on the subjects. Before entering into a description of the effects of the drug on respiratory infection and accompanying complications, it is desirable to summarize first the data bearing on the toxicity of sulfadiazine. Each of the treated children received 148 grams of sulfadiazine over a period of 15 weeks and this treatment was followed by little sign of toxic reaction. Thus, a transient rash was encountered in only two children. There was no loss of appetite and no vomiting. The average weight for the treated group increased 1.5 pounds, as compared with 1.0 pound in the control group. Although most of the urines examined revealed sulfadiazine crystals estimated at a few to many, with microscopically, a few red blood cells and at times, a trace of albumin, there was no indication of gross bleeding or urinary obstruction. Similarly, none of the bloods revealed important increases in non-protein nitrogen. Furthermore, there was no critical drop in blood count during the period of observation. The red blood cells fluctuated slightly, whereas the average white blood cell count dropped 37 per cent in the treated group and 30 per cent in the control group.

Blood concentration of sulfadiazine. The amount of free sulfadiazine in the blood varied considerably with each individual. The average blood levels for the different subjects fluctuated from 1.9 to 6.9 milligrams per 100 c.c. when the daily dosage was one gram. With increase of the dosage to two grams daily, there was a corresponding increase in the blood level reaching from 3.2 to 13.9 milligrams per 100 c.c. The average blood level was maintained at 3.4 milligrams per 100 c.c. on a daily dosage of one gram and 7.2 milligrams on a daily dosage of two grams.

Effect on infections. Contrary to expectations, the incidence of pneumonia and other serious acute respiratory illnesses ran unusually low during

* During the early part of the study, the blood levels of free sulfadiazine were determined through the courtesy of Dr. Jesse G. M. Bullowa at Harlem Hospital, New York.

the period of study, not only in cottage Iota where the study was conducted, but in the entire institution. In cottage Iota, the differences between the current and past periods were quite marked, as shown in the following tabulation of the number of cases of pneumonia from September through May of each year beginning with 1939.

NUMBER OF CASES OF PNEUMONIA IN COTTAGE IOTA FROM 1939 TO 1943

Month	Past years			Current year
	1939–40	1940–41	1941–42	1942–1943
September	7	0	2	1
October	7	0	3	0
November	3	0	1	0
December	2	0	1	0
January	3	1	4	1
February	8	0	0	1
March	3	7	3	0
April	5	9	0	1
May	3	3	1	4
Total	41	20	15	8

On the basis of past experience in cottage Iota, from eight to 16 cases of pneumonia were anticipated during the test period from December 1942 through March 1943. Instead, only two cases occurred. About a month after the test period, an outbreak of scarlet fever occurred, lasting from April 24 to June 2 and affecting 28 (21.5 per cent) inmates of the cottage. The disease was responsible for three cases of pneumonia during May, as many, in fact, as occurred in the preceding six months.

The relative infrequency of pneumonia during the test period of 1942–1943 was paralleled by a decrease in the incidence and severity of the common acute respiratory infections observed in the cottage. In early December, before drug therapy was begun, there were only few mild instances of acute infections of the respiratory tract, whereas from December 11 to March 25 when sulfadiazine was administered, the number of cases fluctuated considerably. In a general way, they were moderately high during the middle of January and the beginning of March, but fairly low at other times. During the entire period, there were no outbreaks either with severe infections or with high attack rate. This was in contradistinction to the outbreaks in the past when usually they occurred at least once or twice each winter. Very few cases were seen toward the end of the test period and for the first two weeks thereafter. Then, the incidence increased markedly during the latter part of April and in May when scarlet fever occurred.

There were no striking clinical differences between the two groups throughout drug therapy. A purulent nasal discharge or other sign of infection of the upper respiratory tract was observed at some time during the test period in 25 treated and 24 control children. The average duration of

the nasal discharge was somewhat longer in the control group than in the treated, but the differences were not great enough to be considered significant in the small numbers observed.

Acute febrile respiratory infections were observed in seven of the 30 treated children receiving daily drug therapy. One child had two attacks and the others, single attacks, making a total of eight cases for the group. The infections were clinically limited to the upper respiratory passages. In the control group, there were also seven children with a total of eight acute febrile infections. Seven of the infections were limited to the upper respiratory tract, while the eighth case was further involved with lobar pneumonia of the right lower lobe. In this patient, Pneumococcus type XI was isolated from throat smears taken before, during and after the attack. Aside from the one case of lobar pneumonia among the controls, both groups responded in like manner to the acute infections of the respiratory tract observed during the period of drug therapy.

During the time that one gram of sulfadiazine was given daily to the treated group, an outbreak of chicken pox occurred in the cottage. From December 22 to February 9 there were 15 cases (11.5 per cent) and these occurred on the following days:

OCCURRENCE OF CASES OF CHICKEN POX IN COTTAGE IOTA

Date of onset	Total number of cases in cottage	Number of cases in study groups		
		Total	Treated group	Control group
December 22	1	0	–	–
23	1	0	–	–
January 1	1	0	–	–
3	1	0	–	–
8	1	1	1	0
9	4	2	1	1
10	2	2	1	1
12	2	0	–	–
19	1	0	–	–
February 9	1	0	–	–
Total	15	5	3	2

Five cases of chicken pox were observed among the 60 children in the study, three among the treated and two among the control children. They all appeared within a period of three days and were mild in both groups, without manifestation of secondary bacterial invasion.

From the foregoing clinical observations it is apparent that there were no significant differences between the treated and control groups in their response both to the common acute respiratory infections and chicken pox prevalent during the period of daily drug therapy. With the exception of a single case of lobar pneumonia in the control group, the infections were mild and uncomplicated by serious secondary bacterial complications. The infrequency of severe bacterial infection during the test period militated

against a satisfactory clinical test of their prevention by the prophylactic daily use of sulfadiazine.

The immediate post-therapy period was clinically uneventful. There were no acute febrile respiratory infections in either study group for the first two weeks following discontinuation of daily drug therapy. Later, however, four cases of moderate severity occurred within 10 days, three in the previously treated group and one among the control children. All of these infections were confined to the upper respiratory tract.

About a month after the cessation of daily therapy, an outbreak of scarlet fever occurred, as mentioned above, with an attack-rate for the cottage of 21.5 per cent. During the epidemic period from April 24 to June 2, there were five cases in the treated group and two in the control group. The illnesses were mild in six of the affected children and severe in one, a treated child who developed pneumonia at the onset of the disease. He died three weeks later with an extensive bronchopneumonia. Cultures taken before and after death yielded hemolytic streptococci and Pneumococcus type XI. It is interesting that the latter organism was not only recovered from throat cultures from time to time, but by actual test proved to be resistant to sulfadiazine, whereas the former was susceptible to the drug.

Discussion

The present study differed from the one conducted during the preceding year in the administration of sulfadiazine. In the previous study, the drug was prescribed as soon as symptoms of respiratory disease appeared, since early treatment was the chief expedient. From that experience it was learned that the early adoption of drug therapy may be valuable and beneficial depending upon the susceptibility of the bacteria involved, the dosage prescribed, the duration of treatment, and the tolerance and need of the patient for the drug.[1, 2]

In the present study, sulfadiazine was administered continuously, the purpose being the prevention of bacterial infections of the respiratory tract during the expected period of greatest respiratory morbidity. However, despite the use of the drug for 15 consecutive weeks during the four months of the year when severe infections are usually most prevalent, there were no serious outbreaks for a satisfactory clinical trial of the prophylactic value of the drug. The infections encountered, with the exception of a single case of pneumonia, were relatively mild in both treated and control children, and they appeared to be unaffected by the use of the drug. Under the conditions that prevailed, therefore, no particular advantage was gained by the prolonged application of the drug. In this connection it may be of interest to recall similar studies in rheumatic fever, where the continuous use of sulfanilamide appears to reduce the number of exacerbations, presumably the result of the drug on the prevention of streptococcal infections.[4, 5, 6, 7, 8, 9, 10, 11, 12]

With the progression of the study, several questions, speculated upon by

previous workers as well, presented themselves, and to a measure at least answers have been forthcoming. Foremost among these questions has been the cumulative toxicity of the drug. The evidence obtained in this study reveals that speaking in general terms, it may be said that the toxic reactions stimulated by sulfadiazine need not deter its prolonged use if proper precautions are followed. Secondly, the question of drug sensitization has also arisen, and a partial answer has been obtained. Although none of the children presented any signs interpretable as sensitization, the conclusion should be that the condition may indeed occur, as others have reported, but that its frequency for sulfadiazine, at least, is of low order. In addition, there remain questions, both clinical and academic, pertaining to acquired bacterial resistance. These will have to await presentation and discussion for their appropriate places in subsequent reports on the collateral bacteriological studies described in sections 2, 3, and 4 which follow.

Summary and Conclusions

1. Sulfadiazine was administered to 30 children for a period of 15 weeks, from December 1942 through March 1943, to determine its effect on the bacterial flora of the nasopharynx, and on the frequency, severity, and complications of acute respiratory infections.

2. During the first half of the study, daily dosage was one gram and in the latter half, the dosage was doubled. The concentration of free sulfadiazine in the blood averaged 3.4 mg. per 100 c.c. with the lower dosage, and 7.2 mg. per 100 c.c. with the higher dosage.

3. For purpose of control, 30 additional children comparable with those receiving drug were observed under the same living conditions.

4. Recognizable toxic reactions attributable to sulfadiazine were negligible. Changes in red and white cells and non-protein nitrogen of the blood were all within the range of normal variations. Sulfadiazine crystals and a few microscopic red blood cells were observed commonly in the urines.

5. The respiratory infections encountered were pneumonia, the common cold and chicken pox.

6. There were no significant differences in the frequency and severity of the infections of the respiratory tract observed in treated and control groups.

7. The clinical infections in both groups were few, relatively mild and, with one exception, were not complicated by virulent bacterial invasion so that any prophylactic or therapeutic effect of the drug was not readily demonstrable.

8. Significant changes in the bacterial flora of the nasopharynx were observed and will be described in sections 2, 3, and 4 of the report.

Acknowledgment

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THE EPIDEMIOLOGY OF ACUTE RESPIRATORY INFECTIONS CONDITIONED BY SULFONAMIDES.

II. GROSS ALTERATIONS IN THE NASO-PHARYNGEAL FLORA ASSOCIATED WITH TREATMENT *

By L. A. JULIANELLE † and MORRIS SIEGEL, *New York, N. Y.*

THAT sulfonamides exert considerably greater retarding effect on the development of bacteria than viruses, has been too common an experience to require more than passing mention. Consequently, it is not surprising, as previous reports from this laboratory have already indicated,[1, 2, 3] that in the administration of sulfadiazine little influence was observed on the incidence and severity of acute respiratory infections presumably of viral etiology. In organizing the clinical studies, therefore, it became important to measure the effects of drug treatment in terms of changes and fluctuations in the bacterial flora of the upper air passages. In the present communication it is proposed to describe some of the bacteriological observations made in physically normal children under prolonged treatment with sulfadiazine.

METHODS

As described earlier [3] two groups, each composed of 30 feebleminded children, were under constant observation from November 1942 to July 1943. One group was given sulfadiazine daily from December 11 to March 25 (15 weeks), the dosage consisting of one gram per diem during the first two months and two grams per diem during the remainder of the time. The second group, while maintained under identical conditions of living, received no drug. The basis on which the children were selected, the method of drug administration during health and infection, and related procedures have already been described in detail [3] so that they need not be repeated in this place.

Simultaneously with the clinical observations, throat cultures were made at first in a variety of ways and culture media. It was found in time, however, that adequate information might be obtained by seeding blood-agar plates with material collected by pharyngeal swab, so that this was the only technic continued. For about the earlier half of the drug treatment, cultures were made in relays covering the 60 individuals within a week, but this schedule was subsequently extended to 10 day intervals. The cultures were incubated in the customary manner and identification of the cultivable organisms was effected by the usual methods.

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It was originally planned to quantitate the data, so that the incidence of the different species might be calculated on a numerical basis. As desirable as this may be, no practical or reliable method was found. The procedure finally adopted was to estimate the number of colonies developing on the blood-agar plates and from this estimation to derive an approximate ratio of the different species present.

Experimental

The pharyngeal cultures taken prior to the period of drug treatment were intended primarily for orientation. They also served to establish the important fact that both groups of children were as similar as could be expected regarding their throat flora. To illustrate that this statement is justified, figure 1 is submitted with a representation of the results observed

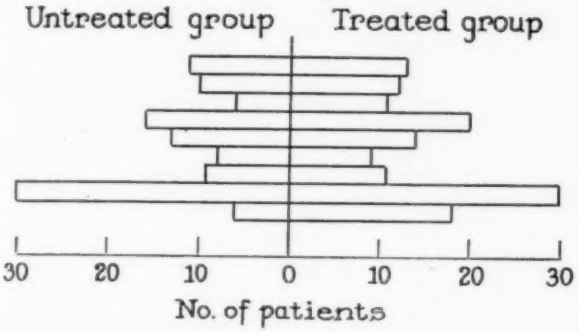

Fig. 1. Distribution of different bacteria before drug treatment. Reading downward the organisms represented are: Streptococcus alpha, beta, gamma, Pneumococcus, Staphylococcus, Sarcina, Diphtheroids, Neisseriae and *H. influenzae*.

in the preliminary cultures. Each bar represents the number of individuals carrying the organism designated. A glance suffices to show that while there were minor variations between the two groups, the general character of the graphs is similar for both groups of children.

Results of the cultures. During the 15 weeks of drug administration, 9 pharyngeal cultures were seeded from each individual in both treated and untreated groups. The data bearing on the distribution of the different species have been plotted in figure 2. Using the same scheme as adopted in figure 1, the columns themselves represent successive cultures, while the height of the column indicates the number of individuals carrying the organism in question. Analysis of the data reveals that except for Neisseriae and hemolytic streptococcus, the different organisms were recovered in somewhat greater numbers in the treated group. Although there are a number of fluctuations apparent for all the species, it can be said that in general the variations are more or less similar for both groups of children. The outstanding exception to this statement is the striking alteration in frequency of the Neisseriae, which will be discussed later at greater length.

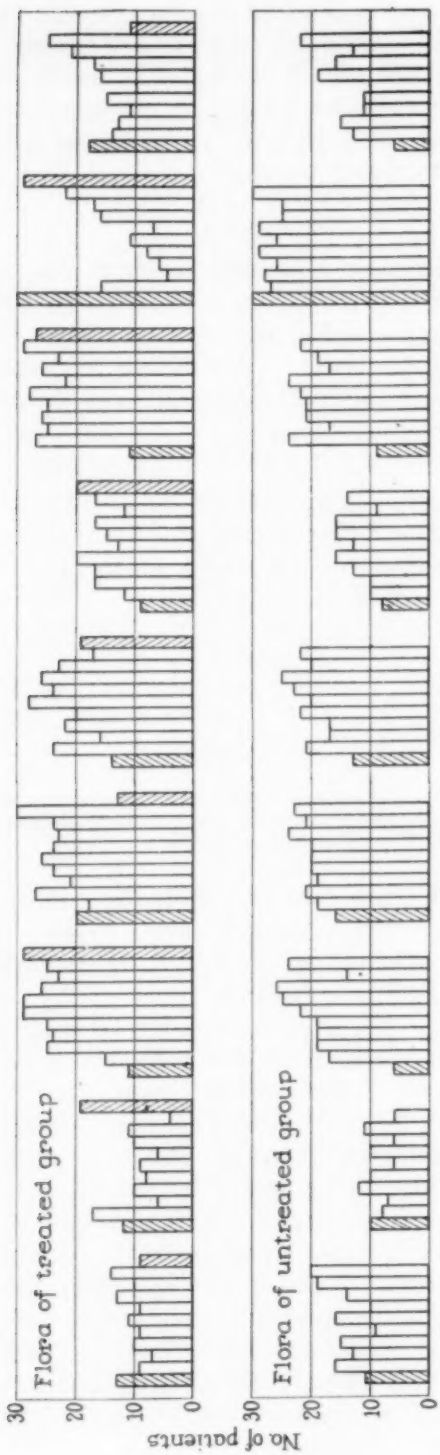

FIG. 2. Frequency of different organisms in treated and untreated children. For each species, the first hatched bar represents the preliminary cultures taken a week before therapy, the white bars the results of nine successive cultures during the therapeutic period, and the last hatched bar in the treated group the cultural results obtained four days after cessation of therapy.

TABLE I

Frequency of Different Bacterial Species in Pharyngeal Cultures

Organism	Group	Incidence	
		Numerical	Percentile
Neisseriae	Control	250	15.2
	Treated	116	7.1
Diphtheroids	Control	207	12.5
	Treated	249	15.2
Pneumococcus	Control	200	12.2
	Treated	229	14.0
Staphylococcus	Control	200	12.2
	Treated	219	13.3
Streptococcus gamma	Control	197	12.0
	Treated	244	14.9
H. influenzae	Control	155	9.4
	Treated	163	10.0
Streptococcus beta	Control	153	9.3
	Treated	103	6.3
Sarcina	Control	129	7.8
	Treated	149	9.1
Streptococcus alpha	Control	83	5.0
	Treated	91	5.5
Miscellaneous	Control	72	4.4
	Treated	75	4.6
Total	Control	1646	100
	Treated	1638	100

To help simplify presentation of the data, a summary protocol (table 1) is appended to illustrate the relative frequency of the species during administration of sulfadiazine. If, first of all, the occurrence of any species is considered as a single unit, irrespective of whether it was the same or different organism, then it may be said that there was a total of 1646 isolations in the control group as compared with 1638 in the treated group. Among the controls, Neisseriae with 250 isolations were the most frequent of all the organisms encountered, with the order of frequency proceeding with diphtheroids, pneumococcus, staphylococcus, indifferent streptococci, Streptococcus gamma, *H. influenzae, Streptococcus hemolyticus,* Sarcina, *Streptococcus viridans,* and finally, a scattering of miscellaneous forms. In the treated group the diphtheroids with 249 isolations predominate with indifferent streptococci, pneumococcus, staphylococcus, *H. influenzae,* Sarcina, Neisseriae, Streptococcus beta and alpha, and, last of all, the miscellaneous bacteria in the order named. The discrepancies immediately apparent between the treated and untreated children are found in both the

Neisseriae and hemolytic streptococci. In the untreated group the Neisseriae are more than twice as frequent, and the hemolytic streptococci were half again as frequent as in the treated group. The implication is obvious that sulfadiazine induced a bacteriostatic effect on the former organisms, and although not so definite, there is a suggestion of similar though less extensive activity on the latter.

Other organisms than those classified above were identified from time to time in the cultures. Because their number was not great and their frequency not regular, no need was felt for discussing them. That the records may be kept complete, it is desirable to catalogue the species encountered. Most numerous of the rarer forms were the gram-positive cocci of the tetragenus group. Occasionally, the colon bacillus was isolated, as were monilia, streptothrix, unidentified fungi, and members of the subtilis group which were in all probability merely contaminants. Because of their rare appearance, no statement can be made as to whether sulfadiazine had any effect on their presence or incidence. It is interesting that Friedländer's bacillus was never isolated, as was also true of meningococcus.

It seems desirable at this point to comment briefly on the individual species isolated during the course of observations. Of the streptococci, the indifferent or gamma forms were most commonly encountered in both the drug-treated and untreated children. They ran consistently higher in the individuals receiving sulfadiazine, and the drug manifested no measurable reduction on their incidence. Next in frequency came the hemolytic or beta variety. In this case, the cocci were more numerous in the untreated group. The viridans or alpha Streptococcus appeared in the least number of patients, only rarely (two occasions) occurring in more than half of either group. Their incidence was lower in the untreated individuals and the drug was apparently unable to reduce their numbers significantly. In all three organisms there were fluctuations with successive cultures in the proportion of drug-treated children carrying the cocci, but these were irregular and in general simulated the changes observed in the untreated group.

Pneumococci were found with a high degree of regularity throughout the survey in both treated and untreated children alike. It will be observed in figure 2 that these organisms ran moderately higher in the drug-treated group, and in both cases they proved to be present in a high proportion of the total flora. In spite of the lengthy course of sulfadiazine, there was no visible gross effect on the number of pneumococci cultivable from the treated individuals. This came in the nature of a surprise since it had been anticipated that a reduction would sooner or later make itself manifest. A study of the types involved, however, clarified completely what appeared to be a paradox. Owing to the number of experiments undertaken and the space required to describe and explain the observations, it seems wiser to reserve all discussion of this organism for a later communication.

Staphylococci were also present in a large number of the cultures. Their frequency ran slightly higher in the treated children, but their fluctuation

from culture to culture paralleled that observed in the untreated group. Consequently, it is felt that this species was not affected by the prolonged exposure to sulfadiazine resulting from the daily administration. It may be of interest to compare the ratio of *aureus* and *albus* strains in both groups of children. Thus, the proportion of *aureus* to *albus* strains in the untreated group was approximately 1:3.4 and 1:3.2 in the treated group. The predominance of *albus* strains was to be anticipated, perhaps, since speaking in general terms, the large majority of staphylococci harbored in the normal throat are saprophytic which in turn are usually, not always, of the *albus* variety. Another point of interest was the proximity of the ratios in both groups of children, which indicates in another way, perhaps, the absence of any action by the drug.

Sarcinae comprised the last of the gram-positive cocci to be described. Their incidence was low, although a trifle greater in the treated children. Apparently they were not influenced by sulfadiazine.

Of the gram-positive rods, the Corynebacteria only require comment. Diphtheroids were present commonly in the throat cultures and they persisted throughout the period of observation. Several weeks after the study was begun, a diphtheria carrier was detected among the treated children. The organism spread rapidly, creating conditions for a more specialized study which will be reported appropriately in a subsequent communication. It may be said that in both instances, however, their frequency was not limited by continuous administration of sulfadiazine.

The gram-negative organisms were represented almost entirely by *H. influenzae* and the different Neisseriae. Members of the Hemophilus group consisted essentially of *H. influenzae*. Occasionally, the hemolytic variety was found, but its presence was neither constant nor numerous. In any case, these organisms did not play a prominent part in the bacterial flora and, as far as could be determined, no effect was induced upon them by the sulfadiazine.

In commenting on the Neisseriae, it must be said that no serious classification of the different species of gram-negative cocci was attempted, chiefly because the action of the drug was generalized and included each variety observed. The data bearing on these organisms are submitted graphically in figure 3 and they show both the reduced distribution in the treated individuals and, more importantly, the changing frequency of gram-negative cocci occurring in the cultures. The height of each column represents the number of children carrying the organisms. In order to illustrate the number of colonies isolated in each culture, each column has been divided to represent growth as ++++, +++, ++, + and ±. ++++ signifies Neisseriae were the predominate organisms of a culture, +++ second in predominance, ++ third, + fourth, and ± fifth or beyond.

Examination of the data indicates that although the frequency of cultures containing gram-negative cocci and the relative number of colonies per culture ran remarkably alike in both groups before the drug was started, there

was a rapid and marked divergence immediately afterwards. In the control children, the distribution of Neisseriae maintained a more or less consistent status in the nasopharyngeal flora, so that they retained their relative prevalence with insignificant variations during the entire period of drug therapy. Among the treated children the predominance of gram-negative cocci fell rapidly, so that within three to seven days after drug therapy began they were not isolated in almost half of the cultures. During the first month

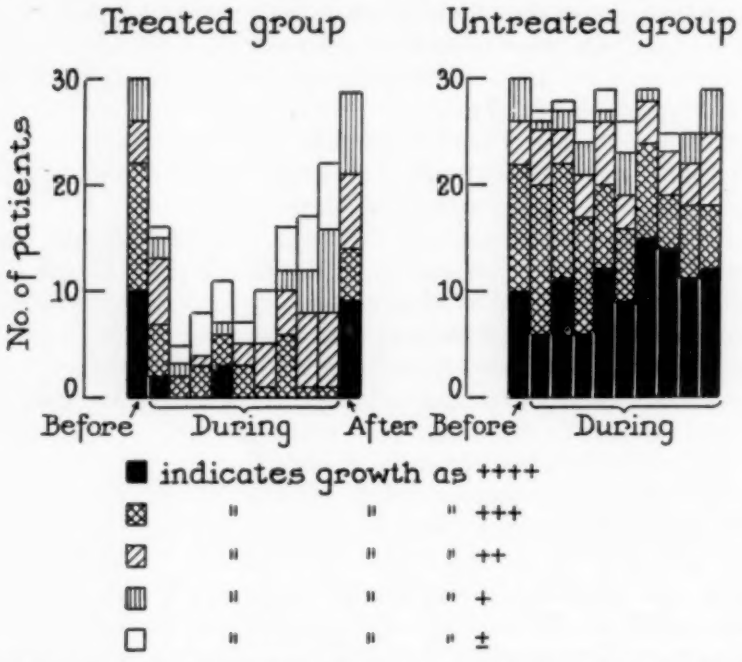

FIG. 3. Distribution of Neisseriae by individuals and their numerical frequency in culture.

of drug therapy, either no colonies or relatively few colonies of gram-negative cocci could be isolated. After that, despite doubling of sulfadiazine dosage, the frequency of positive cultures increased progressively, although the number of colonies per culture still remained low in many instances. Shortly after withdrawal of the drug, the Neisseriae returned to their original frequency. The changes described were so marked and characteristic that most of the treated and control cultures could be differentiated from each other by the relative prevalence of Neisseriae on the blood agar plates.

The striking differences observed between the two groups are summarized in table 2. During the period of drug therapy, the Neisseriae were the prevailing organism in only 2 per cent of the cultures taken in the treated group as compared with 35 per cent of those taken in the control group, and second most numerous in 9 per cent of the treated in contrast to 30 per cent of the controls. Moreover, the gram-negative cocci were completely

TABLE II

Numerical Frequency of Neisseriae in Nasopharyngeal Cultures of Untreated and Treated Children

Degree of Growth	Treated group		Untreated group	
	Number	Per cent	Number	Per cent
++++	5	1.9	106	35.3
+++	25	9.3	90	30.0
++	32	11.8	44	14.7
+	18	6.7	23	7.7
±	36	13.3	11	3.7
0	154	57.0	26	8.7
Total.....	270	100.0	300	100.1

The plus signs may be interpreted as ++++, most numerous of all the different organisms isolated, +++ as second most numerous, etc., while 0 indicates no Neisseriae were isolated.

absent in almost 60 per cent of cultures from treated children as compared with less than 10 per cent for the controls.

Another point of interest concerns the permanency of the disappearance of Neisseriae during continued administration of sulfadiazine. The data analyzed for this purpose are tabulated in table 3. The disappearance has been classified as prolonged, intermittent and transient. By prolonged is

TABLE III

Changes in Neisseriae with Administration of Sulfadiazine

Groups	Total number of children	Disappearance of Neisseriae			No change
		Prolonged	Intermittent	Transient	
Untreated.....	30	0	4	11	15
Treated.....	30	15(6*)	8	1	0

* The continuity in these six individuals was interrupted by a single or two inconsecutive appearances of Neisseriae.

meant failure to recover gram-negative cocci on culture during a period of 7 to 10 weeks; intermittent implies alternating success and failure in the cultivation of Neisseriae; transient indicates failure in a single culture or on two scattered occasions. The data reveal that in 15 or half of the treated individuals the disappearance of Neisseriae was prolonged; to this number must be added six more children whose long run of "negative" cultures was interrupted once or twice by the presence of a few colonies. Also in this group there were eight examples of intermittent and only one of transient disappearance, with not a single child unaffected by the drug. In the untreated group there were no prolonged disappearances of Neisseriae, 4 intermittent, 11 transient and 15 in whom no changes were observed from culture to culture.

The abnormal changes observed among the gram-negative cocci occurring in the pharynx were subsequently related to acquired resistance to sulfadiazine. A few weeks before terminating drug treatment, a number of strains were isolated for the purpose of determining their resistance to varying concentrations of drug. For this purpose, 10 strains were selected at random from the control children and seven from the children who had received the drug. For the sake of brevity, the growth of several strains, considered as typical, have been tabulated (table 4) to illustrate the types of reaction observed. Thus, measuring first the growth in drug-free broth as the maximum for that particular strain, the development in the same broth containing increasing concentrations of sulfadiazine from 1 mg. to 25

TABLE IV

Illustration of Reaction of Neisseriae to Sulfadiazine

Strain number and source	Degree of growth in							
	Drug-free medium	Medium containing sulfadiazine						
		*1	2	3	5	8	12	25
N24—Untreated	++++	−	−	−	−	−	−	−
N26—Untreated	++++	++	−	−	−	−	−	−
P45—Untreated	++++	++++	+++	+++	+++	++	+	−
N29—Untreated	++++	++++	++++	++++	+++	+++	+++	+++
N37—Untreated	++++	++++	++++	++++	+++	+++	+++	+++
R27—Treated	++++	++++	++++	++++	++++	++++	++++	++++
R57—Treated	++++	++++	++++	++++	++++	++++	++++	+++

The degree of growth is indicated by different graduations ranging from maximum (++++) to no growth (−).

* These figures indicate concentration of drug as so many milligrams per 100 c.c. of medium.

mg. per 100 c.c. of medium was noted and graded correspondingly. The assembled data illustrate that susceptible strains (e.g., N24 and N26) were unable to withstand as little as 2 mg. of sulfadiazine per 100 c.c. of broth. A single strain was considered as intermediate or partially resistant to the drug (N45). This strain isolated from one of the untreated children grew poorly to be sure, but in a concentration of 12 mg. per 100 c.c. Resistant strains both from treated and untreated children withstood without appreciable difficulty concentrations of 25 mg. per 100 c.c., the highest concentration to be tested.

The occurrence of resistant strains among the untreated group as well as among the treated requires explanatory comment. During the period of drug treatment the contact between the two groups of children was very intimate, so that strains undoubtedly passed freely between both groups. Thus, in an untreated individual (No. 46) the culture isolated during the time sulfadiazine was administered was so susceptible that it failed to grow in a concentration of sulfadiazine of 2 mg. per 100 c.c. of broth. About a month later, after cessation of the drug in the treated group, another culture isolated from the same child was able to grow in a concentration of

25 mg. per 100 c.c. In this case, the fastness must be interpreted as a likely transfer of a resistant strain to him from one of the treated children.

If the data pertaining to drug-fastness are now summarized (table 5) it is seen that all seven strains isolated from the treated children proved to be resistant to sulfadiazine. Of the 10 strains originating from the untreated children, five were susceptible, one was partially resistant, and four

TABLE V

Summary of Experiments on Resistance of Neisseriae to Sulfadiazine

Strains isolated from	Number of strains and reaction to drug			Total strains
	Susceptible	Intermediate	Resistant	
Untreated group.....	5	1	4	10
Treated group.....	0	0	7	7

equalled the resistance observed in the case of the strains from the opposite group. The important point is that among the subjects receiving sulfadiazine, none of the strains tested was found susceptible. The conclusion seems clear, therefore, that with administration of sulfadiazine, the disappearance of the Neisseriae was due to a susceptibility of the organism to the drug; the reappearance, on the other hand, even under prolonged and increased treatment, was associated with an acquired tolerance or resistance to the drug.

DISCUSSION

The most striking effect observed of the continuous administration of sulfadiazine in physically normal children was brought into evidence by a rapid disappearance of gram-negative cocci from the nasopharynx. The sequence of events observed was first the actual disappearance of Neisseriae from the majority of treated individuals, then their gradual return in spite of doubly increasing the dosage of sulfadiazine and finally, the demonstration in vitro of the drug susceptibility of the organisms from the untreated children as contrasted with the drug resistance of those from the treated children.

Less striking and perhaps only suggestive was the evidence gathered on the inhibition of hemolytic streptococci. Perhaps because these organisms were never numerous, it may be that the action of sulfadiazine was not so readily detected. Yet the more frequent occurrence of these cocci as well as their greater numbers per plate in the untreated children suggests a possible but not extensive effect of the drug on hemolytic streptococci. This possibility is now under study in healthy carriers.

It is further interesting that in spite of numerous fluctuations in the frequency of the different organisms, the total isolations from both groups of children ran remarkably close. This may have been due entirely to chance.

Yet, one wonders, nevertheless, whether the fluctuations may not represent a state of balance attained by a numerical compensation of one species over another; in which case, there might be a factor of some kind operative under certain undefined conditions to limit the population of different bacterial species multiplying in the same environment. Such a factor might then explain not only the presence or absence of specific organisms, but even the ascendency of one species on the suppression of another.

From either the medical or public health aspect, the results on the gram-negative cocci reaffirm a repeated clinical observation that where sulfonamides are effective, their action is prompt and usually conclusive. It is not necessary, therefore, to continue administration, provided the dosage is adequate, if during the first few days the effect is questionable or nil. Of epidemiological interest is the disturbing fact that with prolonged use of the drug, the previously susceptible strains not only become resistant, but they may even spread through an exposed population.

Summary and Conclusions

1. Prolonged treatment of physically normal children with sulfadiazine causes changes in the bacterial flora of the throat, as demonstrable on blood-agar plates.

2. The most striking change is a rapid disappearance of the gram-negative cocci.

3. This action is transitory, however, since the cocci return in their original frequency in spite of continued treatment.

4. Associated with the reappearance of the gram-negative cocci, it is possible to show an exalted tolerance for the drug on the part of the bacteria.

5. Although the numerical incidence of pneumococcus remains more or less constant during treatment, there is evidence, not now described, of great changes in immunological types.

6. The effect on hemolytic streptococci is not conclusive, but the data suggest a partial inhibitory action by sulfadiazine.

7. Other organisms as staphylococci, Streptococcus alpha and gamma, diphtheroids, Sarcina, tetragenus and *H. influenzae* are not noticeably affected under the conditions outlined.

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THE EPIDEMIOLOGY OF ACUTE RESPIRATORY INFECTIONS CONDITIONED BY SULFONAMIDES. III. EFFECTS OF TREATMENT ON THE ORGANISM AND CARRIER OF DIPHTHERIA *

By L. A. JULIANELLE † and MORRIS SIEGEL, *New York, N. Y.*

INTRODUCTION

DURING the course of observations on the changes in the bacterial flora of the upper respiratory passages associated with prolonged administration of sulfadiazine, the organism of diphtheria was unexpectedly isolated from the throats of two children receiving the drug. As will be recalled from the preceding reports in this investigation,[1, 2] a study was in progress on 60 children, half untreated in any way and the other half treated for 105 consecutive days with sulfadiazine. The purpose was to determine what effect this treatment might have on acute respiratory infection and in what way it might influence the organisms cultivable from the nasopharynx. With the appearance of *C. diphtheriae,* careful clinical examination of the carriers was made but no abnormal signs or symptoms were uncovered. Skin tests with diphtheria toxin (i.e., Schick test) were performed in the usual manner and they indicated that all the children under observation were so-called "immune." It was decided, therefore, to allow dissemination of the organism to proceed without interference in order to ascertain both its mode of spread and its behavior under sulfonamide therapy.

Upon questioning of the medical officers in charge at the institution, it was learned that in the past an occasional case of nasal diphtheria, which was not severe in character, had been encountered in the cottage housing the children under study. Presumably, then, the original source of the organism was in some of the children who, while living in the same cottage, were not included in the present survey. If this assumption is correct, an explanation is readily furnished for the absence of the organism in the earlier cultures of the children studied.

EXPERIMENTAL

Dissemination of C. diphtheriae during treatment. The administration of sulfadiazine was begun on December 11 (1942), and for the 240 cultures studied in relays up to January 4, *C. diphtheriae* was never observed. On

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† Died, August 12, 1944.

that day the organism was isolated for the first time in two individuals, both receiving the drug. From then on, cultures were studied at approximately 7 to 10 day intervals on blood agar plates and Loeffler's serum slants until the end of the survey. During that period it became possible to follow the spreading of the organism among the different individuals, which by the end of the study included 30 children, or exactly one half of the total subjects in the original study. Of these, 17 were in the treated and 13 in the untreated group. A total of 38 strains were isolated from the treated boys and 30 from the untreated boys. In addition, the organism was isolated from two attendants assigned to the cottage. That an idea of the mode of spread may be visualized, cultures yielding *C. diphtheriae* have been plotted in the order of their occurrence. Examination of figure 1 illustrates this diagrammatic representation.

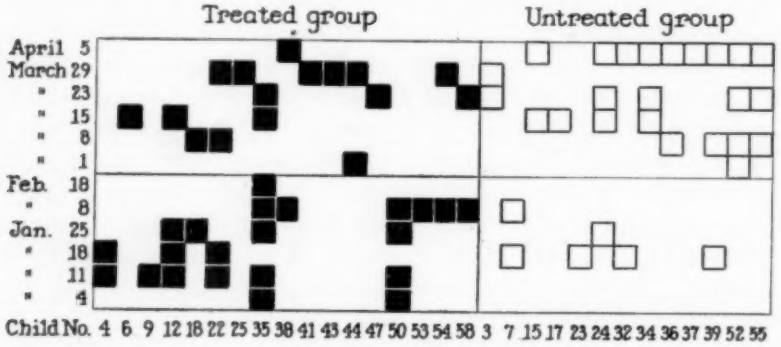

FIG. 1. Dissemination of *C. diphtheriae* in children under study.

Of clinical interest is the fact that in spite of the prolonged administration of sulfadiazine, the organism was able to spread freely among the children studied. The indications are, therefore, that under clinical conditions of treatment, sulfadiazine must be considered ineffectual in controlling the growth of *C. diphtheriae*. That this conclusion is justified will be demonstrated subsequently by experimental procedures.

Classification of the strains.[3] It is perhaps a natural assumption since the population studied was a relatively closed group, that all the cultures isolated were derived from a single common strain. Nevertheless, a bacteriological study was made of the greater number of the organisms recovered during the period of observation. Thus, 18 strains derived from the untreated children, 26 strains from the treated children and two from attendants in service in the cottage were utilized for purposes of classification. It is only fair to state that in certain cases the strains were probably duplications in the sense that they were isolated from the same individuals but at different times. This was done intentionally to bring out any possible deviations occurring between early and late isolations. If, however, a correction is desirable on this account, it might be more accurate to speak of 14

strains from treated children, 13 strains from untreated children, and two from the attendants. The reaction of these strains in media containing phenol red as indicator, serum and various carbohydrates was first determined and a summary of these reactions is to be found in table 1. All 46 strains behaved in similar fashion, causing acid and coagulation in dextrose, and acid in variable degrees of intensity in dextrin. In lactose, sucrose, mannite, glycogen and starch, the growth was accompanied by no visible change in reaction.

TABLE I

Reaction of 46 Strains of *C. diphtheriae* in Carbohydrates

Strains		Reaction in						
Number	Source	Dextrose	Dextrin	Lactose	Sucrose	Mannite	Glycogen	Starch
18	Untreated group	All AC	All A	NR	NR	NR	NR	NR
26	Treated group	All AC	All A	NR	NR	NR	NR	NR
2	Attendants	All AC	All A	NR	NR	NR	NR	NR

AC—Indicates acid and coagulation. A—Indicates acid only. NR—Indicates no reaction.

In classifying further the 46 strains studied, a note was made of their microscopic appearance, effect on rabbit blood (in agar plates), character of growth on tellurite agar, and toxigenicity as measured in the guinea pig. Microscopically, all the strains suggested the *mitis* form. On rabbit blood agar plates, all but two strains were hemolytic, and these formed an area of methemoglobin around each colony. One of the two strains was isolated from an untreated and the other from a treated child. On tellurite agar, the hemolytic strains were typical of the *mitis* variety, while the two producing methemoglobin suggested the *intermedius*. The colonial appearance of the latter differed in some respects from the typical form, so that there is a hesitancy in labeling the two strains definitely as such.

Virulence of the strains. Tests for toxigenicity were carried out on the basis of screening tests. Pools were made of three or four cultures by emulsifying the growth from Loeffler slants (18 hours' incubation) with 1.0 c.c. of broth. The suspensions were then pooled and from the pool 1.0 c.c. was taken and injected subcutaneously into guinea pigs weighing approximately 250 grams. Although it is realized that the dosage adopted was large, it was deliberately selected because from the clinical histories a low toxicity was suggested. In case the animals survived, all the strains composing the pool were regarded as non-toxigenic. In case of death, an autopsy was performed. If organisms were cultivable and stainable from the original site, if a gelatinous edema surrounded the area of inoculation, and if the adrenals appeared to be enlarged and hemorrhagic, the pool was broken down into its component strains and retested as individual cultures. The results of the tests for toxigenicity are summarized in table 2. Thus, of the 18 cultures derived from the untreated children, six were characteris-

TABLE II

Classification of 46 Strains of *C. diphtheriae*

Strains		Microscopic appearance	Effect on rabbit blood	Growth on tellurite	Toxicity per guinea pig
Number	Source				
18	Untreated group	All *mitis*	1 methemoglobin 17 hemolytic	1 *intermedius*? 17 *mitis*	6 toxic 12 non-toxic
26	Treated group	All *mitis*	1 methemoglobin 45 hemolytic	1 *intermedius*? 25 *mitis*	1 toxic 25 non-toxic
2	Attendants	All *mitis*	2 hemolytic	2 *mitis*	2 non-toxic

Effect on rabbit blood was determined by growth on blood agar.

The two strains listed as questionable *intermedius* were suggestive of this variety but the characteristics were not completely conclusive.

The toxic strains in the untreated group represent six isolations from three individuals or, actually, only three different strains.

tically toxigenic and 12 nontoxigenic. However, since the six strains were isolated from three individuals at different times it can be said that actually only three different strains produced toxin. Of the 26 strains isolated from the treated group, only one was toxigenic. It may be of interest to add that after survival of the guinea pigs receiving pooled cultures was established, all the animals were subsequently tested for immunity to diphtheria toxin. Within a period varying from 10 days to three weeks after the injection of cultures, the guinea pigs were inoculated intraperitoneally with 10 M.L.D. of toxin. In each case, death followed within 24 hours with typical signs of diphtheria intoxication. This, then, is another way of demonstrating the nontoxigenicity of the strains in question.

TABLE III

Recapitulation of Characteristics of *C. diphtheriae*

Strain	Group	Reaction on			Toxigenicity
		Rabbit blood	Tellurite	Sugars	
No. 23	Untreated	Methemoglobin	*intermedius*?	Typical	+
No. 38	Treated	Methemoglobin	*intermedius*?	Typical	+
No. 24	Untreated	Hemolysis	*mitis*	Typical	+
No. 3	Untreated	Hemolysis	*mitis*	Typical	+
All others (42 Strains)	Both	Hemolysis	*mitis*	Typical	0

A recapitulation of the characteristics of the different cultures (table 3) indicates that the four toxigenic strains divide themselves in two groups of two strains each. In the one group, the cultures produced methemoglobin on rabbit blood agar, suggested the *intermedius* form on tellurite agar, and gave typical reactions in sugars; in the other group, the cultures were hemolytic, suggested the *mitis* form on tellurite agar, and gave similar

reactions in sugar. The remaining strains studied were all avirulent, hemolytic, and appeared to be typical of the *mitis* variety, both on tellurite agar and in sugars.

On first analysis, it appears that the 46 strains partition themselves into three varieties: methemoglobin-producers and toxigenic, hemolytic and toxigenic, hemolytic and nontoxigenic. On second consideration, however, the thought cannot be dismissed that the dissimilarities enumerated are perhaps minor and that they may represent not essential differences, but evidences of degradation or variation from an originally common or identical strain.

Reaction of C. diphtheriae to sulfadiazine. In continuing with the investigation, it was found of interest as a co-related problem to determine the effect of sulfadiazine on the organisms isolated. For this purpose, 16

TABLE IV

Growth of *C. diphtheriae* in Broth Containing Sulfadiazine

Strains		Control	mg. of sulfadiazine per 100 c.c. of broth						
Number	Source		5	8	12	25	50	75	100
B24	Untreated group	++++	++++	++++	++++	++++	++++	++++	++++
N24	Untreated group	++++	++++	++++	++++	++++	++++	++++	++++
3	Untreated group	++++	++++	++++	++++	++++	+++	+++	+++
23	Untreated group	++++	++++	++++	++++	+++	+	+	+
32	Untreated group	++++	++++	++++	+++	++	++	++	++
N32	Untreated group	++++	+++	+++	+++	+++	+++	+++	+++
7	Untreated group	++++	++++	++++	++++	++	++	++	++
15	Untreated group	++++	++++	+++	+++	++	+	+	+
C38	Treated group	++++	++++	++++	++++	++++	++	++	++
322	Treated group	++++	++++	++++	++++	+++	++	++	++
R22	Treated group	++++	++++	++++	++++	+++	++	++	++
A.8	Treated group	++++	++++	++++	++++	+++	+++	+++	+++
K.8	Treated group	++++	++++	++++	++++	++++	++++	++++	+++
D58	Treated group	++++	++++	++++	++++	++++	++++	++++	++++
P58	Treated group	++++	++++	++++	++++	+++	++	++	++
235	Treated group	++++	++++	++++	++++	+++	++	++	++
Park No. 8		++++	++++	+++	+++	++	++	+	+

strains were selected at random and their reaction to the drug was first studied in vitro. For orientation, similar tests were performed with the Park No. 8 strain. The tests were performed by adding to beef-infusion broth, concentrations of sulfadiazine varying from 5.0 mg. per 100 c.c. to 100 mg. per 100 c.c. Inoculations were made with 0.1 c.c. of 18–20 hour broth culture. Similarly, broth not containing sulfadiazine was inoculated with each strain. The growth obtained in this case was regarded as ++++, and this was used as a standard for comparison for growth of the same organism in medium containing sulfadiazine. The experiment was repeated in parts, two to four times, with variable results, due presumably to both the growth-promoting factors for *C. diphtheriae* and the sulfonamide-blocking substances contained in the medium. The data pertaining to the experiment will be found assembled in table 4. It will be seen that although minor variations in the degree of tolerance are evident, the statement can justifiably be made that the strains tested were resistant to sulfadiazine. One

other point worthy of comment is that in several cases, strains isolated both early and late from the same individuals were studied for possible increased tolerance to the drug without, however, detecting any appreciable differences.

Effect of sulfadiazine on toxin. Since no bacteriostatic action of importance was demonstrable, experiments were next projected to establish any influence of the drug on the toxic properties of the organism. This was done by first determining the effect on preformed toxin and secondly, by observing the effect on the elaboration of toxin by cultures themselves resistant to the drug. In the first experiment, diphtheria toxin * in quantities of 10, 20 and 50 M.L.D. were each mixed with sulfadiazine to give concentrations of the drug of 5, 8 and 12 mg. per 100 c.c. The mixtures were incubated at 37° C. for four hours, when they were inoculated subcutaneously in guinea pigs weighing about 250 grams. This made a total of nine animals, all of which died within 24 hours. Autopsy revealed typical signs of intoxication. Although the experiment might have been extended to include greater concentrations of sulfadiazine and longer periods of incubation, the preliminary results discouraged further trials. Under the conditions of the experiment, then, no effect was observed by the action of sulfadiazine on diphtheria toxin.

In the second experiment, the effect of sulfadiazine on the elaboration of toxin was studied. Three strains isolated from individuals under observation were used, and for control purposes, the Park No. 8. Different concentrations of drug varying from 5 mg. to 50 mg. per 100 c.c. of medium were added to broth which was then inoculated individually with the four strains. After nine days' incubation, filtrates obtained from the cultures were inoculated into guinea pigs to detect the presence of toxin. It is necessary to say only that compared with the results in media without drug, sulfadiazine appeared to have no inhibitory influence on the elaboration of toxin.

Effect of sulfadiazine on experimental infection. In parallel with the two preceding experiments, a study was made of the therapeutic value of sulfadiazine in active infection by *C. diphtheriae.* Cultures grown on Loeffler's medium for about 18 hours were harvested in 1.0 c.c. of broth. This was then inoculated subcutaneously into two guinea pigs followed immediately by intraperitoneal injection of 0.05 gram of sulfadiazine. Administration of drug was then continued at this dosage twice a day until the experiment was terminated. The strains tested were the Park No. 8 and No. 23 isolated in this study. For control study, a single animal was inoculated with virulent culture but was denied sulfadiazine. Other controls consisted of guinea pigs similarly treated with an avirulent culture and drug, and two other animals injected with drug alone over a period of five days. The results of the experiment disclose a failure on the part of sulfadiazine to protect guinea pigs from death under the conditions stated. The animals died in intervals varying from 24 to 72 hours. The animals in-

* The diphtheria toxin was kindly furnished by Dr. O. R. Povitzky and Mr. C. K Greenwald of the Bureau of Laboratories of the New York City Health Department.

jected with avirulent culture and drug, or drug alone suffered no ill consequences. Death in each case was that typical of diphtheritic infection. The evidence indicates, as the in vitro studies had already suggested, that sulfadiazine is not effective in diphtheritic infection. This conclusion is considered to be a confirmation of similar studies reported on the use of sulfonamide in experimental infection of guinea pigs.[4]

Discussion

The studies recorded in this report on *C. diphtheriae* were not intended as a classification of the species. Rather was it the purpose to establish the variety of the strains isolated during the present survey and then to continue with the object at hand, of ascertaining their response to sulfadiazine. Consequently, having identified the large majority (44 of 46 strains) as the *mitis* variety, with the two remaining strains as questionable *intermedius,* or better perhaps as indeterminate, it was still considered possible that all the cultures may have originated from a single strain. That only four of 29 strains tested were toxigenic was not surprising, because the experience over the past several years in the cottage housing the children has been that clinical infections were rare and limited to a relatively mild, nasal affection. Even in these cases, the strains must be considered weakly toxigenic because of the large dosages employed for the injections. Evidence corroborating this experience is perhaps furnished by the fact that despite the dissemination of the organism in 30 of the 60 children under observation and in two attendants, there was not a single instance of clinical infection, even in the four children carrying toxigenic strains.

The observation that the organism was recovered in children under sulfadiazine treatment suggested immediately its tolerance to the drug. In the one case of a toxigenic strain in a child of the treated group, the inference was also obvious that the drug did not inhibit formation of toxin. The tests performed in vitro on bacteriostasis, elaboration of toxin, and inactivation of preformed toxin succeeded in establishing as facts the impressions gained by clinical observation, since in all three no effect was exerted by sulfadiazine in various concentrations. Similarly, the treatment of experimental infection in guinea pigs by large dosage of drug failed to affect the usual course of fatal intoxication. It is interesting to point out that in a preceding report [2] it was likewise shown that prolonged administration of the drug in children had no effect on the frequency or numbers of the closely allied organisms, the diphtheroids. The drug-fastness of the different strains of *C. diphtheriae* isolated from treated and untreated children, or at early and late stages of treatment was approximately the same, indicating an original, high resistance which was not demonstrably increased by continuous administration of sulfadiazine.

Summary and Conclusions

1. Continuous administration of sulfadiazine did not prevent either the dissemination of *C. diphtheriae* among exposed children or its repeated recovery from throat cultures.

2. Sixty-eight strains of *C. diphtheriae* were isolated from 30 children, 38 from 17 children under treatment with sulfadiazine, and 30 from 13 children not so treated, and two other strains from attendants.

3. A classification was made of 46 strains, 18 from 14 untreated children, 26 from 13 treated children, and two from attendants.

4. With the exception of two questionable *intermedius* or indeterminate strains, the organisms were of the *mitis* variety.

5. It is possible that the indeterminate strains represent variations from a common parent strain.

6. Bacteriostatic tests performed with sulfadiazine revealed that 16 tested strains isolated from the children under study, as well as the Park No. 8 strain were resistant to high concentrations of the drug.

7. Sulfadiazine under the conditions outlined above did not inactivate preformed toxin, nor prevent the elaboration of toxin.

8. In experimental infection, administration of sulfadiazine as described was ineffectual as a method of treatment.

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THE EPIDEMIOLOGY OF ACUTE RESPIRATORY INFECTIONS CONDITIONED BY SULFONAMIDES.

IV. TRENDS IN PNEUMOCOCCAL TYPES INITIATED BY DRUG TREATMENT *

By L. A. JULIANELLE † and MORRIS SIEGEL, *New York, N. Y.*

IN an earlier communication,[1] the occasion was taken to comment on the observation that judged by superficial examination, the continual use of sulfadiazine exerted little effect on the frequency of pneumococcus in the throat cultures of physically normal children. It was intimated, however, that underneath the surface this organism was actually participating in a profound process reminiscent of natural selection. It is proposed to submit in the present report a detailed account of the alterations observed and to describe the correlated experiments undertaken to explain their occurrence. The general method employed in handling the children, half under sulfadiazine treatment and the other half untreated, the manner of taking cultures and carrying them through, etc., have all been described elsewhere.[2]

EXPERIMENTAL

Cultures were taken preliminarily to establish the bacterial flora of the nasopharynx under so-called normal conditions, so that in this way a base line could be drawn of the types present before treatment was begun. The types of pneumococci isolated were ultimately recognized by the *quellung* reaction but in determining types, the method adopted as simplest and most accurate was to immerse a swab carrying the inoculum from the patient's throat directly into "pneumococcus broth" containing horse blood. The medium was then incubated together with the swab, overnight. On the following morning (about 16 hours) the mixed broth culture was used for direct microscopical typing.‡ This method was found far superior to typing either from blood agar plates or from inoculated white mice because of three advantages: (1) virulent as well as avirulent organisms were recovered; (2) a much higher proportion of multiple types was detected than by the other two methods; and (3) because of the directness of the technic, considerable time and manipulation were saved. As will be brought out later, a certain number of strains could not be classified into types, in which case the diagnosis of pneumococcus was assured by mouse virulence, bile solubility, and

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From the Division of Infectious Diseases, The Public Health Research Institute of The City of New York, Inc.

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‡ The antisera used for typing was graciously supplied by the Lederle Laboratories and the Bureau of Laboratories of the New York City Health Department.

in some instances by demonstration of capsules. Not all cultures were mouse virulent, but it was felt that even in the absence of this attribute reliance could be placed upon the other two properties.

The cultures taken preliminarily before beginning administration of sulfadiazine disclosed types VI, XI, XII, XVIII, XIX and XXI to be present among both groups of children, although it is felt that with the paucity of data no accurate statement can be made about predominance of types. As already described,[1] pneumococcus was found in great frequency throughout the period of treatment, running somewhat higher for some reason or other among the treated children. Examination of cultures on blood agar plates indicated that sulfadiazine was having little gross effect on its frequency. With the determination of types, however, it soon became obvious that the individual types were undergoing striking changes.

TABLE I

Distribution of Pneumococcal Types during Period of Treatment

Type of pneumococcus	Untreated group		Treated group	
	Number	Per cent	Number	Per cent
I	11	7.7	1	0.5
III	3	2.1	0	—
VI	29	20.4	7	3.8
IX	6	4.2	3	1.6
XI	44	31.0	113	61.4
XII	1	0.7	2	1.1
XV	0	—	2	1.1
XVI	0	—	3	1.6
XVII	1	0.7	0	—
XVIII *	17	12.0	47	25.5
XIX	1	0.7	1	0.5
XXI	3	2.1	1	0.5
XXII	1	0.7	0	—
XXIII	19	13.4	0	—
XXIV	0	—	3	1.6
XXV	6	4.2	1	0.5
Totals	142	99.9	184	99.7

* Serologically related to type 18A or type 44.

Distribution of types during treatment. During the period of treatment, a total of 332 strains of typable pneumococci were recovered, of which 142 came from the untreated children and 184 from the treated children. In addition, there were 12 untyped strains from the former and 15 from the latter. In the untreated group, the predominant types in their order of frequency were: XI, VI, XXIII, XVIII, I, IX and XXV, with an unimpressive scattering of types III, XII, XVII, XIX, XXI and XXII. The rates of incidence are shown in table 1. Thus, type XI comprised about 31 per cent, type VI about 20 per cent, type XXIII about 13 per cent, type XVIII about 12 per cent, type I, 8 per cent, and types IX and XXV, 4 per cent each, while the remaining 9 per cent was made of the miscellaneous types.

Among the children given sulfadiazine, trends in types began to manifest themselves quite early; types XI and XVIII became more and more frequent almost to the exclusion of all other types, accounting between themselves, in fact, for roughly 87 per cent of the total types demonstrated. The order of frequency in this group was in marked contrast to that observed in the control group. Thus, type XI comprised 61 per cent of the strains isolated, type XVIII, 26 per cent, type VI, 4 per cent, types I and XXV, less than 1 per cent each, and scattered types made up the remaining 8 per cent (see table 1). These consisted of types IX, XII, XV, XVI, XIX, XXI, XXIV and XXV. Interestingly enough, some of the types encountered in the untreated group did not occur in the treated children, as, for example, type XXIII. Another comparison of possible noteworthiness is that although the bulk of the individuals studied yielded types with uniformity upon culturing, a few, on the contrary, showed pneumococci only rarely. Thus, in the untreated group, one child (No. 3 below) only once presented a typable strain (VI), another (No. 24) only twice, and a third (No. 20) only three times. Among the treated children, one yielded a type only twice and two others (No. 42 and No. 50) three times.

TABLE II

Occurrence of Multiple Types during Period of Treatment

Combination of	Untreated group			Treated group		
	Total	Types XI and XVIII		Total	Types XI and XVIII	
		Number	Per cent		Number	Per cent
Two types	23	4	17.4	34	28	82.4
Three types	6	2	33.3	5	4	80.0
Totals	29	6	20.7	39	32	82.0

An additional observation of interest regarding the effect of sulfadiazine on pneumococcal types was furnished by an analysis of the cultures containing mixed or multiple types. The data appended in table 2 indicate that in the untreated children 23 or 16 per cent of the recovered types occurred as mixtures of two types and six or 4 per cent were mixtures of three types. These figures compare equably with those from the treated children: 34 or 18 per cent with two types and five or 3 per cent with three types. When the data are broken down, however, it is found that in the control group the mixtures were heterogeneous and consisted of almost any aggregation of the types encountered within the group. In the treated children, on the contrary, the mixtures were more uniform, running predominantly as combinations of types XI and XVIII, so that of the total 39 mixed cultures, 32 or about 80 per cent were of this category.

It may be of interest to introduce at this point a short comment on the possible source and persistence of the types encountered during this survey.

Since 1939, when epidemiological studies on acute respiratory infections were started by this laboratory at Letchworth Village, 23 cases of pneumococcal pneumonia occurred among the 60 children included in the present study. To expedite discussion of the cases, the pertinent details have been summarized in table 3. It will be seen that the 23 pneumonias were distributed among 20 children, since two (19 and 40) were afflicted three and

TABLE III

Previous Pneumococcal Pneumonias and Their Relation to Present (1942–1943) Carrier Types

Type during pneumonia	Number of child	Present group	Date of pneumonia	Recovery of homologous types	
				Same children	Other children
I	60	Treated	April 1941	Not recovered	Occasionally
	13	Untreated	March 1941	Not recovered	
	14	Untreated	March 1941	Consistently	
	19	Untreated	March 1941	Not recovered	
	37	Untreated	Jan. 1942	Once	
IV	43	Treated	Sept. 1939	Not recovered	Never
V	4	Treated	May 1941	Not recovered	Never
	58	Untreated	Oct. 1941	Not recovered	
	5	Untreated	June 1941	Not recovered	
VI	1	Untreated	Jan. 1941	Not recovered	Frequently
	3	Untreated	June 1941	Once	
	43	Treated	May 1941	Not recovered	
	40	Treated	Nov. 1940	Not recovered	
VII	25	Treated	Dec. 1941	Not recovered	Never
XI	40	Treated	April 1941	Consistently	Frequently
XI	29	Untreated	Oct. 1939	Not recovered	Frequently
XIV	33	Treated	Dec. 1941	Not recovered	Never
XVII	21	Untreated	May 1941	Not recovered	Rarely
XVIII	47	Treated	Nov. 1940	Not recovered	Frequently
XVIII	19	Untreated	Feb. 1940	Once	Frequently
XIX	20	Untreated	April 1941	Not recovered	Rarely
XXII	15	Untreated	Oct. 1941	Not recovered	Rarely
XXIII	19	Untreated	March 1940	Consistently	Occasionally (Untreated group only)

two times, respectively, but with different types. The types involved in the infections were type I, five times, type VI, four times, type V, three times, types XI and XVIII, each twice, and types IV, VII, XIV, XVII, XIX, XXII and XXIII, each once. During the current observations, at intervals varying from three years to 10 months after their pneumonias, only six of the children were found to carry the same types as those responsible for their previous illnesses. In three instances (3, 19 and 37) the homologous type was recovered only a single time, and in the other three (14, 19 and 40) it was demonstrated consistently. Curiously enough, child 19 with three pneumonias regularly yielded the type responsible for an earlier (i.e., the second), not a later infection.

Upon examination of the data for the incidence of the above types among the other children included in the study, it was found that types VI, XI and XVIII were present frequently, types I and XXIII, occasionally, types XVII, XIX and XXII, only rarely, while types IV, V, VII and XIV were never observed throughout the eight months of repeated typings. It appears, therefore, that the types found during the present survey cannot be entirely related with the previous pneumonias and that the distribution exhibits vagaries of types appearing in any large population.

Reaction of types to sulfadiazine in vitro. An explanation for the curious predominance of the types in the nasopharynx of the treated children was readily obtainable when experiments were undertaken on the acquired resistance of the different types to sulfadiazine. In projecting this survey an effort was made to study (1) the susceptibility of the types occurring only

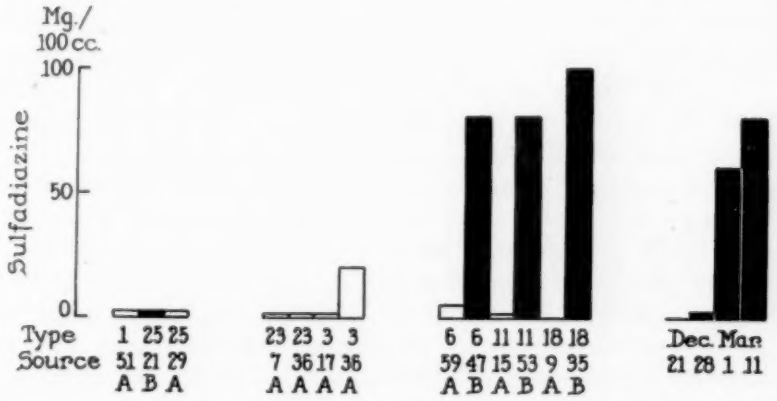

FIG. 1. Resistance of pneumococcal strains to sulfadiazine. Black represents strains from treated group (B); white, from untreated group (A). Dated data on extreme right refer to type XI strains isolated at different times from the same treated individuals.

in the untreated children (e.g., types III and XXIII); (2) the susceptibility of types appearing sporadically in and disappearing abruptly from the throats of treated children (e.g., types I and XXV); and (3) the reaction of types encountered consistently in both groups (e.g., types VI, XI and XVIII).

In determining susceptibility, sulfadiazine was added to "pneumococcus broth" in varying concentrations, and inoculation of this medium and proper controls was accomplished with 0.5 c.c. of a 1:10 dilution of an 18 hour broth culture. Observations were recorded each day for three days. Since it was desired to acquire comparative figures, it was not felt necessary to seek the possibly greater accuracy obtainable with media free of sulfonamide-inhibiting substances. As a matter of fact, the results to be described were reproduced on several occasions within remarkable proximity.

In order to illustrate the nature of the results obtained, some of the data have been plotted in figure 1. Thus, in answer to the first question

implied above, two strains each of types III and XXIII recovered from different individuals of the untreated group were unable to tolerate completely as little as 2 mg. of sulfadiazine per 100 c.c., except for one strain of type III which did grow poorly at a concentration of 10 mg. Types as I and XXV, which appeared sporadically and disappeared quickly from the flora of treated children but persisted longer in the untreated children, were all highly susceptible. In no instance did they withstand more than 2 mg. of sulfadiazine per 100 c.c. Finally, the types occurring consistently in both groups (VI, XI and XVIII) were found to be susceptible (2.0 to 5.0 mg. per 100 c.c.) when isolated from untreated children, but appreciably resistant (80 to 100 mg. per 100 c.c.) when recovered from treated children. The evidence seems clear, therefore, that in prolonged administration of sulfadiazine, strains of pneumococcus may acquire an exalted degree of fastness to the drug.

However, in order to illustrate that the drug resistance might indeed be an acquired characteristic developing with continued application of sulfadiazine, an experiment was done to demonstrate this concept. Different cultures of the same type were isolated from the same individuals at successive intervals during the course of sulfadiazine treatment. Thus, a strain of type XI was isolated December 21, 10 days after treatment was begun. At this time, it was unable to grow in medium containing 1 mg. of sulfadiazine per 100 c.c. One week later (December 28) growth was observed in 2 mg. per 100 c.c. Approximately two months later (March 1) the organism grew in 60 mg. per 100 c.c., and 10 days later (March 11) the tolerance had increased to 80 mg. of drug per 100 c.c. (figure 1).

Comparative virulence of strains and antibody titers. Homologous types taken from both treated and untreated children were injected intraperitoneally in white mice in dilutions ranging from 10^{-1} c.c. to 10^{-6} c.c. of 18 hour broth cultures. The results revealed that irrespective of group derivation or of resistance to sulfadiazine, the strains of the same types were of the same degree of infectivity, suggesting not only a common source for the types in question, but, as has been pointed out by other workers, not even a loss in virulence or in serological specificity for strains refractory to sulfonamides. It is noteworthy that the virulence of all tested strains of types XI and XVIII was uniformly low for mice.

The continual presence of virulent strains in both groups of children stimulated a certain interest and speculation on the complete lack among the children of clinical infection due to these types. This was particularly true of the strains of type I which were lethal for mice in dilutions of 10^{-6} c.c. of culture. Attempting to obtain a partial explanation of this paradox, all the sera were tested for antibody. These tests included in each case, capsule-swelling of the homologous types isolated during the study, agglutination tests, and precipitation tests for the species-specific polysaccharide * ("C"-substance). In certain selected instances, protection tests

* This preparation was generously supplied by Dr. Michael Heidelberger.

were also performed. In each test, the strains isolated from the children themselves were used as antigens. No antibody was detected by these means.

In this connection, it may be pertinent to mention observation on three children whose histories antedate the present study by two years. One of the children was given injections of type I specific carbohydrate [3] which rendered the skin reactive to the soluble specific substance but did not stimulate mouse protective antibodies. Within a year or less this child including two others not previously "immunized" suffered pneumonias due to pneumococcus type I. Following convalescence, all three possessed protective antibodies to a titer of 1000 lethal doses. Approximately two years after the pneumonias, or during the present study, antibody was again sought for but not detected by the reactions of agglutination, precipitation, *quellung* and protection.

TABLE IV

Chronological Appearance of Type I Pneumococcus

Group	Child	Date of appearance								
		2/23 and before	3/5	3/15	3/25	4/19	5/10	5/20	5/31	6/10
Untreated	14	−	+	+	+	+	+	+	+	+
	28	−	+	−	−	−	−	−	−	−
	34	−	+	+	−	−	−	−	−	−
	37	−	+	−	−	−	−	−	−	−
	51	−	−	+	+	+	+	+	−	−
	7	−	−	−	−	−	−	+	+	+
	29	−	−	−	−	−	−	−	+	−
	39	−	−	−	−	−	−	−	+	−
	47	−	+	−	−	−	−	−	−	−
Treated	22	−	−	−	−	−	+	−	−	−
	49	−	−	−	−	−	+	+	+	−
	18	−	−	−	−	−	−	+	−	−
	40	−	−	−	−	−	−	−	+	−

Line of separation in both groups divides the individuals carrying Type I during period of treatment from those detected after cessation of treatment.

Incidence of type I. About two and one-half months after beginning drug administration, type I was abruptly encountered in the routine cultures. Never observed in the cultures preceding February 23, it appeared on March 5, the next date of culture, in four boys, all in the untreated group. The presence of this unusual carrier type can probably be explained by an outbreak of pneumonia due to type I pneumococcus in 1941, in the cottage housing the boys as described in earlier studies from this laboratory.[3] It seemed a good opportunity not only to chart its dissemination, but also to observe its infectivity among both treated and untreated children. The chronological course of the spreading is given in table 4. It will be seen that during the period of treatment it was recovered in five boys of the un-

treated and in only one of the treated group. Since the strain was found to be highly sensitive in vitro to the action of sulfadiazine (2.0 mg. per 100 c.c.) the deduction, at first glance, is perhaps reasonable that the drug may have directed the distribution of the organism among the children. Moreover, following withdrawal of sulfadiazine, type I was found in five boys of the untreated and four boys of the treated group. In two of the untreated subjects (14 and 51) the organism persisted for several weeks, while in all others its appearance was transitory. Since this was true in both groups, it is difficult to believe that sulfadiazine per se was responsible for the transiency of this type.

Distribution of types following treatment. The data reviewed above suggest that with prolonged administration of sulfadiazine pneumococcal types become drug-fast and the more susceptible types tend to be elim-

TABLE V

Distribution of Pneumococcal Types after Cessation of Treatment

Type of pneumococcus	Untreated group		Treated group	
	Number	Per cent	Number	Per cent
I	10	7.2	6	4.4
III	3	2.1	0	—
VI	38	27.1	38	27.5
IX	17	12.1	8	5.7
XI	14	10.0	18	13.0
XV	2	1.4	0	—
XVIII	27	19.3	32	23.2
XIX	3	2.1	0	—
XXII	0	—	3	2.2
XXIII	14	10.0	20	14.5
XXV	12	8.6	13	9.4
Totals	140	99.9	138	99.9

inated in the host. In this way, the distribution becomes less extensive so that only a few types of the many originally present remain. In order to acquire further information on this phenomenon, it was decided to continue with the determination of types after withdrawing sulfadiazine until a comparable number of typings had been performed. The figures obtained in the survey will be found in table 5. Since, however, the contrast between the typings during and after treatment is so great, it has been found more advantageous to present the data diagrammatically also in figure 2. During the later period 140 types were encountered in the previously untreated group and 138 in the previously treated group. An analysis of the types indicates that the former strains consist of type VI as predominant, with the order of frequency as types XVIII, IX, XI, XXIII and XXV, these comprising about 85 per cent of the total strains. The latter strains have lost the overwhelming predominance of types XI and XVIII (87 per cent) and this has been compensated by increases in types VI, XXV and XXIII, the last

of which had never been recovered during the period of treatment. It is obvious that with cessation of drug there has been a marked tendency towards a broader distribution of types, and whereas some are still more frequent, the ratios are not so exaggerated as previously. The more generalized distribution of types with better approximation towards that occurring in the control subjects lends support to the belief that prolonged treatment has a restrictive influence on the incidence and distribution of pneumococcal types.

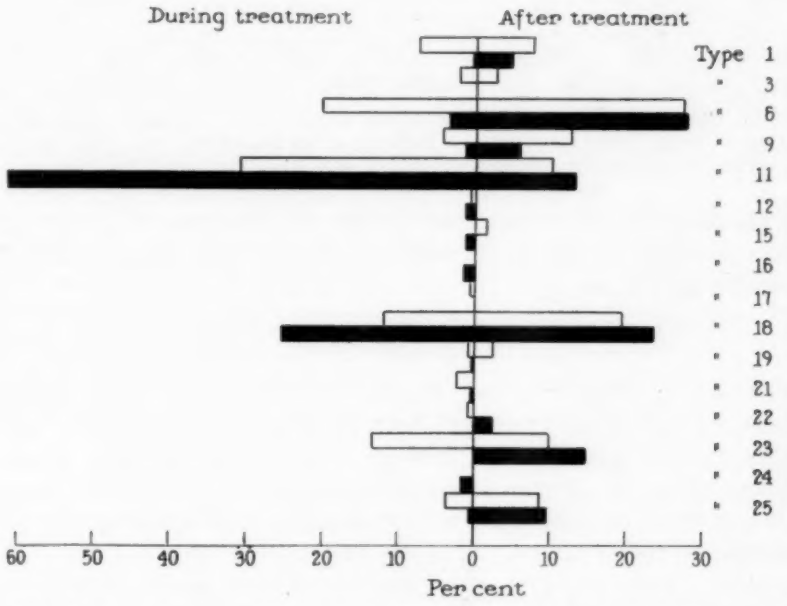

FIG. 2. Distribution of pneumococcal types. Black represents strains from treated group (B); white, from untreated group (A).

Of equal interest in this connection is an analysis of the multiplicity of types found in the same individuals after the period of treatment. As the data summarized in table 6 reveal, mixed types were detected in the treated group 34 times, 26 times as dual types and eight times as triple types or

TABLE VI

Occurrence of Multiple Types after Cessation of Treatment

Combination of	Untreated group			Treated group		
	Total	Types XI and XVIII		Total	Types XI and XVIII	
		Number	Per cent		Number	Per cent
Two types	29	3	10.3	26	6	23.1
Three types	7	1	14.3	8	4	50.0
Totals	36	4	11.1	34	10	26.5

more (i.e., on one occasion four types). Of the total mixtures, the combination of types XI and XVIII was found only 10 times (about 29 per cent) in the treated group. This is in sharp contrast to the incidence ob-

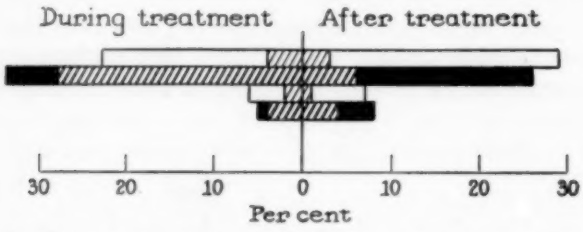

FIG. 3. Combinations of mixed pneumococcal types. Two upper bars represent mixture of two types; lower bars, three types. Hatched gives mixture of types XI and XVIII; solid, mixture of other types. Black for treated and white for untreated group.

served previously of 32 times out of 39 (82 per cent) and it is more in keeping with observations on the diminution of these two types as sulfadiazine was withdrawn (figure 3).

DISCUSSION

A number of observers have reported in the past on the incidence and distribution of pneumococcal types both in disease and in healthy carriers.* There appears to be little need, however, for comparing their results with this report, since the present study was conducted with both a highly susceptible and confined population for the purpose of establishing the effect of sulfadiazine on the organism. The essential contribution has been the effect of this drug on the distribution of the types occurring in the healthy nasopharynx. The evidence from other sources as well [5, 6, 7, 8] appears to be conclusive that with prolonged administration, certain strains acquire an exalted fastness to the drug and they, therefore, remain despite continued treatment even with increased dosages. The susceptible strains succumb or disappear and, in this way, they contribute to the greatly disproportionate frequency of the resistant types. Yet with the drug-fastness there is no concomitant loss either of virulence or specificity of the strains involved. This immediately brings up the question of the potential effect resistant strains may eventually have on the epidemiology and therapy of pneumococcal infection. Experiments are at present in progress to elucidate this possibility, but information thus far acquired is too fragmentary to allow comment.

The lack of infection in the presence of virulent types as well as absence of antibody demonstrable by the methods used offers opportunity for speculation. The continued absence of pneumococci in certain individuals, as pointed out above, despite their intimate contact with perpetual carriers suggests a possible barrier in these individuals which may prevent the im-

*A recent excellent review by Finland [4] covers the literature on this subject with thoroughness.

plantation of pneumococci in the upper air passages. It may be that in some similar manner infection may be suppressed even by virulent strains already present in the tissues. The data suggest to the writers that except, perhaps, when promoted by poorly understood conditions as preëxisting morbidity, debilitation, lowered resistance, exposure, trauma, etc., pneumococcal infection is precipitated not by the individual's carrier types, but by types suddenly acquired from extraneous sources.

Summary and Conclusions

1. Under prolonged sulfadiazine administration in physically normal children, pneumococcal types may acquire a high degree of resistance to the drug.

2. With resistance, there is a striking shift in predominance of types due to elimination of strains not so readily becoming fast.

3. Despite their fastness, the strains retain their virulence and specificity.

4. With discontinuation of drug treatment, the incidence of types tends towards a more normal distribution.

5. Precipitating, agglutinating and protective antibodies were not found in either treated or untreated children.

6. Lack of clinical infection by virulent carrier types was frequently unrelated to either drug treatment or detectable circulating antibody.

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NOTES ON 250 CASES OF SUBACUTE BACTERIAL (STREPTOCOCCAL) ENDOCARDITIS STUDIED AND TREATED BETWEEN 1927 AND 1939 *

By Saul R. Kelson, M.D., and Paul D. White, M.D., F.A.C.P.,
Boston, Massachusetts

In order to understand more fully the clinical picture of subacute bacterial (streptococcal) endocarditis,† to determine the effects of treatment prior to the intensive use of the newer chemotherapeutic drugs, and to establish a baseline of prognosis particularly as a means of evaluating therapy, we have analyzed the records of 250 patients with this disease in certain Boston hospitals ‡ and in private practice § from January 1927 to March 1939.

Although excellent reviews of this disease have been published in the past and collections of cases assembled, as in the writings of Libman and Friedberg,[1] Blumer,[2] Morrison,[3] and Christian,[4] it was thought necessary to cover the years immediately prior to 1939 with a large enough series of cases studied in one community for adequate comparison with clinical findings and therapeutic results in that same or similar environment since 1939.

Such an analysis should guide us reliably as to the outlook for the definitely diagnosed case of this infection as seen in the days before the newer chemotherapy; although we agree that there may be a different prognosis in certain mild and usually clinically undetectable instances of the disease, we have *not* included any such cases in the present analysis because of their uncertainty.

The great majority of the present series of 250 patients had rheumatic valvular disease as a background; a few had congenital defects, including five instances of patency of the ductus arteriosus. Only clinically definite cases were included in this study; all had cultures positive for the nonhemolytic streptococcus, either of the alpha (viridans), or, rarely, the gamma

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† The separation of bacterial endocarditis into "acute" and "subacute" forms, according to the causative organisms, the presence of a primary infective focus and of previous heart impairment, the duration of the disease, the height of the fever, etc. is generally useful but by no means exact. The *Streptococcus viridans* may cause a fulminating infection, and a usually virulent organism like the beta hemolytic streptococcus a lingering one. "Subacute" infections may rarely attack hearts without evidence of antecedent disease, and the bacteria of the "acute" variety may implant on impaired valves. Embolism sometimes kills abruptly after a few weeks or even days of a typically "subacute" course; not infrequently, fever spikes to 105° F. in a case of "endocarditis lenta." Designating the organism, with or without the addition of the term "acute" or "subacute," is preferable to using one of these terms alone.

‡ The Massachusetts General, Beth Israel, Peter Bent Brigham, and Massachusetts Memorial Hospitals, to whose staffs we express our indebtedness and gratitude for permission to include their cases.

§ Of Dr. Paul D. White and Dr. T. Duckett Jones. To Dr. Jones we herewith express our appreciation for permission to refer to his cases.

(anhemolytic) variety. In this series of patients there were 161 males (64.4 per cent) and 89 females (35.6 per cent). The average ages of males (35.2 years) and females (25.7 years) and of the group as a whole (31.8 years) and the distribution of patients according to age are noted in chart 1. The youngest patient was two and one-half years of age and the oldest was 78.

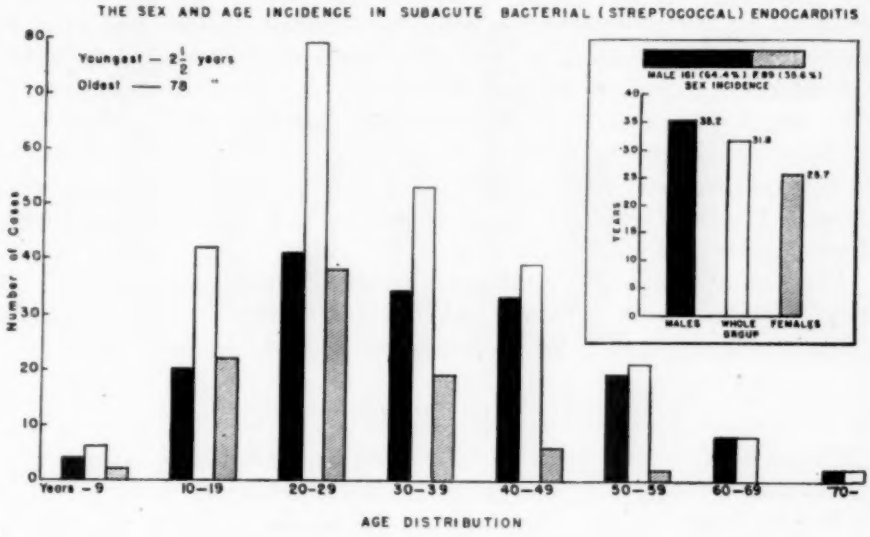

CHART 1.

PART I—DIAGNOSIS AND CLINICAL RELATIONSHIPS

The Clinical Picture. Subacute bacterial endocarditis presents a remarkably varied clinical picture, with signs and symptoms changing with the manifestations of the three underlying processes: infection, embolism, and intrinsic cardiac damage. The disease may begin mildly, with irregular progression of disability due chiefly to the infection itself, resulting in increasing malaise, fever, pallor, and anorexia. It may arise suddenly, with the occurrence of an embolism while the patient has been in apparently good health (though close questioning will disclose, as a rule, a preceding period of at least slight malaise). At times—as in some cases following tooth extraction—the infectious factor may be intense from the start, with chills and high spiking fever. Nearly always, however, these two elements, infection and embolism, mix, with embolism complicating and aggravating the course of infection. The third factor, that of intrinsic cardiac damage, relates both to the preëxisting cardiopathy and to the changing heart lesions of the present illness; the systemic infection, resulting in fever, anemia, and at times nutritional deficiency, reacts upon the heart, which itself may be attacked also by embolism. Changing heart murmurs, increase in heart size, and the common occurrence of varying degrees of failure are the principal manifestations of this third underlying process.

Chart 2 presents the frequency of certain salient clinical features of subacute bacterial (streptococcal) endocarditis. The percentage of incidence of heart murmurs refers to the findings at the time of entrance into the hospital; murmurs developed later in the only two patients in whom they were not heard on admission. The percentage of the other findings is based on their incidence over the period of known observation—during the hospital stay, and—so far as information could be obtained—before and after that time. The incidence of these clinical features would have been found to be greater, of course, if careful observation had been recorded over the entire length of the illness. Splenomegaly, clubbing of the fingers, and petechiae (along with heart murmurs and fever, both present in the course of every case studied) have been considered the most typical findings of the disease. The triad was found to be present in 13.1 per cent of the patients; 6.1 per cent showed none of the three.

Differential Diagnosis. A large number of diseases figure in the differential diagnosis of subacute bacterial endocarditis. These conditions, as they were considered in the present series of cases, are tabulated below:

More Commonly

Grippe	Subarachnoid hemorrhage
Rheumatic fever	Brain tumor
Renal calculus	Brain abscess
Meningococcus meningitis	Cerebral hemorrhage
"Pleurisy"	Central nervous system syphilis
Pulmonary tuberculosis	Latent syphilis
Pneumonia	"Angina pectoris"

Less Commonly

Acute appendicitis	Sinusitis
Gall-bladder colic	Undulant fever
Perforated peptic ulcer	Typhoid fever
Coronary thrombosis	Typhus fever
Tuberculous meningitis	Pregnancy
Lumbago	Perinephric abscess
Neurosis	Subphrenic abscess
Miliary tuberculosis	Pyelonephritis
Encephalitis	Hyperemesis gravidarum
Poliomyelitis	Idiopathic peritonitis
Bronchitis	Sarcoidosis
Bronchiectasis	Echinococcus cyst
Lung abscess	Portal thrombophlebitis

Grippe was the most frequent mistaken diagnosis before or at the time of hospital admission; just how often true grippe had *preceded* the onset of

the bacterial endocarditis could not be learned. Malaise, pallor, and elevation of temperature in these patients with heart murmurs and commonly with histories of rheumatic infection in the past, repeatedly suggested rheumatic fever. In view of the great frequency of cerebral embolism in sub-

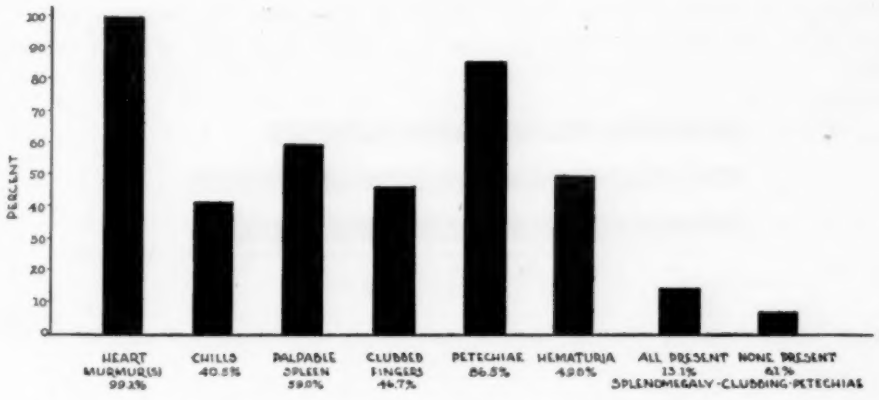

CHART 2. The incidence of certain salient clinical features in 250 cases of subacute bacterial (streptococcal) endocarditis.

acute bacterial endocarditis, it is not surprising that intracranial diseases should appear so prominently on the list.* In one case the right cerebellum of a patient was operated upon in futile search for an abscess. The diagnosis of pneumonia was made often because of the occurrence of chills and fever. Pain resulting from splenic infarction frequently prompted a diagnosis of "pleurisy." Costovertebral pain and hematuria suggested renal calculus. Intra-abdominal embolism led to the diagnosis of an acute surgical emergency: in five instances appendectomies were performed, in one a cholecystectomy, and in another a laparotomy was done for a suspected perforated peptic ulcer. "Fever of unknown origin" was commonly diagnosed, and search made for undulant fever, typhoid, subphrenic abscess, portal thrombophlebitis, etc.† In one striking instance, the lung fields were so studded with infarcts in a patient whose infection complicated patency of

* Syphilis of the central nervous system and elsewhere was diagnosed as the primary disease or as an accompanying condition because of falsely positive serological tests. Without histories or definite signs of syphilitic infection, patients gave positive tests, but at autopsy presented no lesions of syphilis; such tests are most misleading in those with aortic regurgitation without previous known rheumatic fever or chorea. Two particularly interesting later cases—with underlying heart disease of known rheumatic etiology—showed positive serological tests on admission (in one, a blood test had been negative shortly before the present illness), which became negative after apparent recovery from subacute bacterial (streptococcal) endocarditis following sulfapyridine-heparin therapy.

† A recent case, seen by one of us (S. R. K.) subsequent to the present series, at first had been diagnosed and treated as malaria. The chills and fever, anemia, and splenomegaly of bacterial endocarditis may readily suggest malaria, and the heart murmur may be thought related to the anemia and fever. With the greatly increased present and expected incidence of malaria, as brought from distant battlefronts, this disease will assume more importance in the differential diagnosis.

the ductus arteriosus that a roentgen-ray diagnosis of miliary tuberculosis was made. The amenorrhea often accompanying bacterial endocarditis caused the suspicion of pregnancy in two patients; indeed, one woman with severe heart disease had been sent into the hospital for a therapeutic abortion.

Delay in taking or in repeating blood cultures was the chief factor in delaying recognition of the true nature of the patient's illness. It is an important rule that *fever and malaise in an individual with a heart murmur*

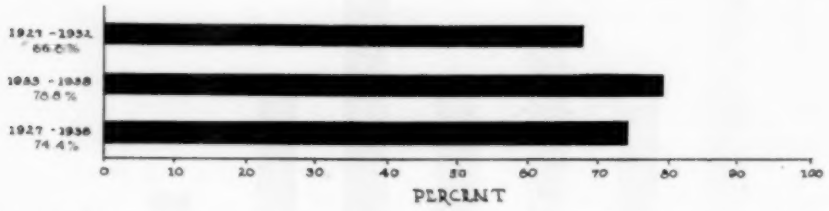

CHART 3. Incidence of positive blood cultures in all cultures taken in proved cases of subacute bacterial (streptococcal) endocarditis.

may mean subacute bacterial endocarditis! It is urgent then (unless another cause is clearly recognized) to confirm or exclude that diagnosis by obtaining repeated blood cultures! At times, as is well known, several cultures need be taken before bacterial growth is obtained. The question as to the ratio of positive to negative cultures (without influence of therapy) in clinically definite cases of subacute bacterial (streptococcal) endocarditis is answered in chart 3. From 1927 to 1932, it is seen, 66.8 per cent of all cultures taken in patients with one or more cultures positive at some time, were positive; from 1932 to 1938 this percentage was 78.8; the percentage for the whole period, 1927–1938, was 74.4. The increased proportion of positive cultures in the second five-year period probably indicates an improvement in bacteriological technic. In the present series, the organisms grew aerobically except in one case, in which six aerobic cultures were negative but two anaerobic cultures showed growth. Though the *Streptococcus viridans* may be recovered from the blood occasionally in other diseases, including rheumatic fever and pneumonia, and frequently following tooth extraction, repeatedly positive cultures, with extremely few exceptions, indicate bacterial endocarditis. In our experience this organism is very rarely a contaminant.

Predisposing Causes. Grippe and upper respiratory infections were recorded as the most frequent precursors of subacute bacterial endocarditis, but it is difficult, as previously noted, to determine whether this was actually grippe (or even the common cold) or an early stage of the endocarditis itself. Next in frequency, some dental procedure, particularly extractions, preceded the onset of the present illness. Here, as has been recognized but too little stressed, the causal relationship is clear. Transient bacteremias, preponderantly with pure cultures of *Streptococcus viridans*—the common organism about the teeth [5]—have been demonstrated repeatedly following

dental procedures. Okell and Elliott [6] found that multiple extractions in cases with marked gum disease were followed by bacteremia in 75 per cent of the instances; single or multiple extractions led to bacteremia in 34 per cent of the cases in which no gingival disease was apparent.* Merely rocking a tooth in an infected gum could discharge bacteria into the blood.[7] In persons with preëxistent valvular or congenital heart disease such organisms usually disappear from the blood quickly and without harmful effect (as in those with normal hearts); but they may implant in crevices of the endocardium, become surrounded with platelets and fibrin, and establish bacterial endocarditis. The following statements are taken from six of the case records in the present series:

"Ulcerated molar extracted, followed by chills and fever."

"Five teeth pulled; chills occurred a few days later."

"Two teeth removed before onset; anorexia and then joint pains followed directly."

"One week before onset, 10 bad teeth removed; pus found in sockets."

"Tooth removed before onset (two weeks later); much digging for retained root."

"Ten remaining teeth removed while patient was in excellent health; one week later, drenching sweats, chills, and fever occurred."

These are striking examples, but other charts mention single uncomplicated extractions preceding the onset of the present illness. Many records also note extensive untreated dental disease, which is likewise hazardous: with such oral sepsis, *Streptococcus viridans* occurs in greatest numbers, and readily enters the blood stream, even in the absence of operative interference.[6]

The frequency of dental work as the predisposing cause of subacute bacterial (streptococcal) endocarditis cannot be determined from the present study because the problem was not specifically investigated in many instances in the history-taking; after looking into the question in a larger series of patients personally seen, one of us (S. R. K.) estimates that in approximately one case in four the disease follows some dental procedure. For persons with known rheumatic or congenital heart lesions, or at times even with murmurs which have been thought to be physiological ("functional"), tooth extractions, less severe dentistry, and untreated oral sepsis carry a definite serious risk! For them these warnings are urgent:

1. Take scrupulous care of the teeth; treat minor disturbances as they arise to avoid major dental procedures.

2. Avoid extractions unless clearly warranted; let no teeth be removed as possible foci of infection for systemic disease unless definite dental lesions are found.

* These cultures usually were taken when the patient was under general anesthesia. It is pointed out [9] that the incidence of post-extraction bacteremia has been found lower, being about 17 per cent, when local anesthetics are used, perhaps because of the vasoconstrictive action of adrenalin contained in the solutions.

3. Avoid harsh or heroic dentistry; not too much attempted at one time and as little trauma as possible.

There is evidence that the use of sulfonamides may prevent or reduce the frequent occurrence of bacteremia after tooth extractions,[8, 9, 10] but further well-controlled studies on large series of patients are needed to determine the value and preferred technic of such medication. At present, it seems desirable to administer a sulfonamide drug active against the *Streptococcus viridans* to those with rheumatic or congenital heart disease at the time of dental extraction. Sulfadiazine, with equal amounts of sodium bicarbonate, begun approximately 10 hours before the planned extraction, with an initial dose of two grams by mouth, followed by four one-gram doses at intervals of four hours, is a recommended schedule. With this, the risk of toxic effect is slight, as is the likelihood that if the disease should nevertheless occur the sulfadiazine will have produced resistance to the action of sulfapyridine (the sulfonamide drug of choice in therapy) on the organisms.*

The onset of subacute bacterial endocarditis was preceded in seven instances by trauma: an automobile injury with severe bruising of the side of the body; an automobile injury resulting in the fracture of a rib; lifting a motorcycle, which caused the side "to go dead"; a fall to a concrete floor 12 feet below; stepping on a nail, with swelling of the foot, which required incision; a fracture of an ankle; a fracture of the skull, with surgical excavation of the clot. The possible causal linkage in these instances is very difficult to evaluate. In each, the accident occurred at a time of usual good health; the frequent mild onset of the disease makes careful questioning concerning the previous state of health extremely important. No other

* Schwartz and Salman [11] found no instance of subacute bacterial endocarditis following a total of 403 extractions among 98 patients hospitalized over a 10-year period for far-advanced rheumatic heart disease, and none after 63 extractions in 36 children out-patients with heart disease, predominantly rheumatic. They reject extraction as a pathogenetic factor and conclude that it is of no greater risk in cardiac than in normal subjects. Taking 6 per cent as the incidence of subacute bacterial endocarditis in susceptible individuals, using an estimated 25 per cent as the proportion of those with the disease in whom a dental extraction preceded its onset, and allowing eight as the total number of extractions during the span of the underlying heart disease, we calculate that the average chance for a susceptible subject to contract bacterial endocarditis after *any one* tooth extraction is one in 533. This risk is not evenly distributed, but varies according to the age group—see chart 1—and with the nature of the underlying process, being less common, for example, with mitral stenosis and unusual in the presence of auricular fibrillation. Statistically, then, the total number of patient-extractions in Schwartz and Salman's series might well show no instance of the disease, and their study does not disprove the factor of tooth extraction in its pathogenesis. The type of disease and the age of the patients make this particularly true, since of the adult sub-group only two did not have mitral stenosis and 45 of the total 60 were "fibrillating"; of their sub-group of 38 children, only one did not have mitral stenosis, and the average age was 12.8 years; the average age in the out-patient group was slightly under 11 years. The risk—one chance in the order of 533—may seem trivial, but from the point of view of patients who have developed subacute bacterial endocarditis following dental extraction—a considerable percentage of those with the disease—the risk has been great indeed, and justifies such simple and unburdensome precautions as outlined. Series showing the absence of subacute bacterial endocarditis following extractions when prophylactic measures have been used, do not, of course, prove the value of these measures, unless the series have been extremely large.

infection or dental procedure to which the disease could be ascribed intervened. In most instances, however, no definite source of the disease can be discovered. Penetrating injuries, such as the punctured foot and fractured skull, provide stronger argument for direct causal relationship, but it is likely that even non-penetrating wounds, with or without obvious inflammation, may set off the crucial transient blood-stream invasion of so common a saprophyte as the non-hemolytic streptococcus. More extensive studies of the varieties and degrees of severity of conditions under which these invasions may occur would help to solve this perplexing problem. Meanwhile, the following hypothesis seems just: injuries occurring when the presence of infection can be excluded by careful history-taking, and followed (without the intervention of known etiological factors such as dental extractions) within a reasonable period (one month would seem a fair limit) by evidence of bacterial endocarditis, may be considered presumptive causative factors in the disease.

Concurrence of Subacute Bacterial Endocarditis and Rheumatic Fever. Views of the relationship between subacute bacterial endocarditis and rheumatic fever have varied widely. Von Glahn and Pappenheimer [12] concluded that, "active rheumatic vegetations are, in persons who have had rheumatism, a necessary and practically constant prerequisite for the implantation of bacteria." Levine,[13] however, writes: "These differences in skin reactions and other suggestive clinical evidences of a certain incompatibility between the rheumatic state and bacterial endocarditis, have led me to think that those individuals who lose their rheumatic predisposition or allergic type of response are the ones who become more susceptible to the development of bacterial endocarditis. The more immune they become to the one, the more susceptible to the other." Other writers have believed that both infections are manifestations of one disease, and that subacute bacterial endocarditis is a virulent form of rheumatic fever.[14]

Among the cases studied, the coexistence of the two diseases has been diagnosed clinically and confirmed at autopsy. Two types of relationship appear to be present:

(1) Subacute bacterial endocarditis may act as a specific or non-specific factor to activate rheumatic fever in susceptible subjects, as tonsillitis, upper respiratory infections, sunburn, trauma, etc., may do. The following case illustrates such an association of the two diseases *:

A man of 22 (E. S.), who had had five attacks of rheumatic fever, resulting in great heart damage, showed characteristic findings of subacute bacterial endocarditis, with four blood cultures positive for *Streptococcus viridans*. Because of a red, tender joint, prolonged auriculoventricular conduction time, and epistaxes, concurrent rheumatic fever was diagnosed, and further indicated by the appearance of auricular fibrillation. All evidences of subacute bacterial endocarditis disappeared after sulfapyridine-heparin therapy; 19 consecutive blood cultures were negative. Slight fever and progressive congestive heart failure, however, pointed to continuing rheumatic

*This and the following case were studied after the original group of 250.

infection. He died in anasarca six months after specific therapy was completed. Autopsy showed an area of clear-cut, definitely healed bacterial endocarditis consisting of typical vegetations, fibrosed and calcified, on the chronically scarred (rheumatic) mitral valve. Cultures, smears, and sections revealed no bacteria. Numerous Aschoff bodies were found in the myocardium.

The following findings in the course of bacterial endocarditis point to concomitant rheumatic fever:

1. Tender, swollen joints.
2. Prolonged auriculoventricular conduction time.
3. Epistaxis.
4. Auricular fibrillation.

(2) Subacute bacterial endocarditis may occur during the course of rheumatic fever. In the following case, as in some others of this group, the superimposed bacterial infection appears related to dental extraction:

Pallor, fever, leukocytosis, elevated sedimentation rate, subcutaneous nodules, and signs of developing mitral and aortic valvular disease established the diagnosis of typical rheumatic fever in this six year old boy (R. DeS.). Eight months after the onset of this illness, an aching, decayed tooth was extracted. One month later chills and high swinging fever occurred, and soon petechiae, splenomegaly, and cultures positive for non-hemolytic streptococci were found. Autopsy two months later showed chronic rheumatic mitral and aortic disease, active rheumatic myocarditis and endocarditis, and the lesion of bacterial endocarditis on the left auricular wall.

The following findings in the course of rheumatic fever point to superimposed bacterial endocarditis:

1. Chills.
2. Visceral emboli.
3. Osler nodes.
4. Repeatedly positive blood cultures.
5. Clubbed fingers.
6. Splenomegaly.*

The Murmurs and Their Interpretation. Chart 4 indicates the cardiac lesions as detected clinically in the 250 cases of subacute bacterial (streptococcal) endocarditis. The unexpectedly high incidence of the diagnosis of chronic rheumatic mitral stenosis as an underlying defect (in 90 cases, with its presence questioned in 22 more) led us to check it against postmortem findings (though precise pathological criteria for the diagnosis of mitral stenosis are wanting). Table 1 shows that in the autopsied 19 patients in whom this lesion (unassociated with stenosis of the aortic valve) had been

* Further discussion of this subject and a presentation of cases of the two diseases together in children are found in the excellent article of Saphir and Wile.[15] Especially illuminating are the comments of Dr. Emanuel Libman, master in the study of bacterial endocarditis, who for a great many years has observed, particularly in necropsy material, the concurrence of the two diseases.

diagnosed clinically, postmortem examination showed actual chronic stenosis to be present only three times; in all five instances in which the diagnosis had been questioned, stenosis was absent; it was present in the two cases in which the diagnosis had been made in conjunction with that of aortic stenosis.

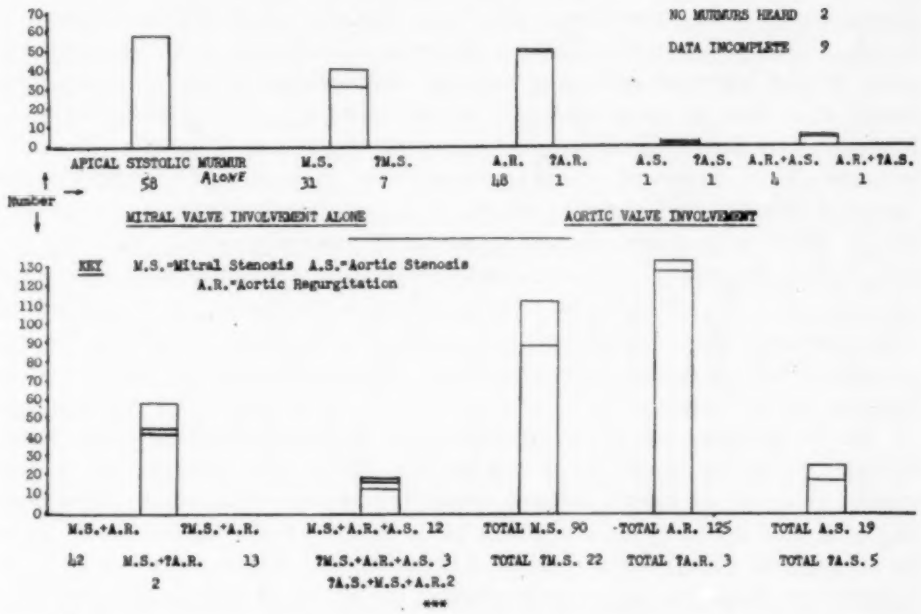

CHART 4. The underlying cardiac lesions in 250 cases of subacute bacterial endocarditis: clinical findings.

TABLE I

The Diagnosis of Rheumatic Mitral Stenosis in Subacute Bacterial Endocarditis

Clinical Findings			Pathological Findings					
Diagnosis	No.	With Aortic Diastolic Murmur	Mitral Stenosis	Mitral Disease (Rheumatic) without Stenosis	Bacterial Vegetations (Mitral)	Mycotic Aneurysm	Perforated Valve Cusp	Normal Valve
Mitral stenosis	19	10	3	10	19	1	3	0
?Mitral stenosis	5	5	0	3	4	1	0	1
?Mitral stenosis ?Austin Flint murmur	1	1	0	0	0	0	0	1
Mitral and aortic stenosis	2	2	2	—	2	0	0	0
No mitral stenosis	30	—	1	—	—	–	–	–

The apical diastolic murmurs which had led to the mistaken clinical diagnosis of rheumatic mitral stenosis were caused, it is believed, by the bacterial vegetations, by aneurysm or perforation of the valvular cusps, or by dilatation of the left ventricle from anemia, infection, and perhaps nutritional disturbance giving relative mitral stenosis (the probable Austin Flint mechanism).* In some cases, aortic regurgitation itself was an important factor. Unless the mitral diastolic murmur is known to have been present *prior to* the bacterial infection and the diagnosis of mitral stenosis then made, it is best to speak only of "mitral disease." Even this diagnosis, however, may then be incorrect, for occasionally patients with mitral diastolic murmurs have shown at autopsy mitral valves free of both rheumatic and bacterial lesions; the dilatation of the left ventricle incident to the present illness (with vegetations on the aortic valve producing or aggravating regurgitation through it) causes a relative mitral stenosis capable of producing the murmur. Overlooking an organic mitral stenosis—an error opposite to that discussed above—occurred but rarely in this series; in 30 of the instances in which mitral stenosis had not been diagnosed it was found at autopsy in only one.

In the presence of aortic regurgitation, apical *systolic* murmurs heard during the course of bacterial endocarditis can not be interpreted as conclusive evidence of mitral disease, either rheumatic or bacterial. The finding of a loud apical systolic murmur prior to the present illness would point to an organic mitral regurgitation; otherwise, the murmur may denote regurgitation through a structurally normal valve. If there has been previous injury to the mitral valve, bacterial vegetations quite regularly localize there: of 44 patients showing lesions of the mitral valve at autopsy, with scarring or vegetations or both, only two presented a scarred valve which was free of vegetations. In the other 42 patients, in whom the mitral valve was a site of bacterial implantation, it was described as showing no evidence of old impairment in three; the heart appeared to have been normal in two of these, and in the third showed patency of the ductus arteriosus and slight coarctation of the aorta.

Among 32 autopsied cases which had shown aortic diastolic murmurs, only two failed to present the lesions of bacterial endocarditis on the aortic valve; one of the two showed a chronically scarred and the other a normal valve. In seven other cases, six with postmortem findings of bacterial vegetations on the aortic valve and one with chronic aortic valvular disease

* It is interesting that in seven of the patients, subsequent to this present series, apparently cured of subacute bacterial endocarditis following sulfapyridine-heparin treatment,[16] apical diastolic murmurs have been found to disappear, both in those with aortic regurgitation and those without it. Alterations in the vegetations in the process of healing, and decrease in size of a previously dilated left ventricle have been considered the explanation for this regression of signs. In five of the successfully-treated patients, also, a high-pitched, musical ("sea-gull") systolic murmur arose at the apex or near it during the course of therapy and later disappeared; it occurred in only one of the cases in which treatment failed, a patient who had shown marked initial improvement.

without vegetations, no aortic diastolic murmur had been heard.* (In only two cases—one with and one without an aortic diastolic murmur—of the autopsied 38 showing aortic valvular involvement, with chronic scarring or bacterial vegetations or both, was a scarred aortic valve found free of vegetations.) In the four autopsied cases in which aortic stenosis had been diagnosed, chronic stenosis was found pathologically in all; it was present, but had not been detected clinically, in two more. Bacterial vegetations described as nearly occluding the valvular orifice had not led to a clinical diagnosis of aortic stenosis in two other cases.

An aortic diastolic murmur heard in a patient with subacute bacterial endocarditis does not necessarily indicate an antecedent aortic regurgitation. Unless the signs of this lesion were found prior to the present illness, such a murmur may result from bacterial vegetations implanted upon a valve scarred insufficiently to have permitted regurgitation, or, as described in four of the present cases, upon a normal valve. Since less severe damage will produce regurgitation than is needed to cause stenosis of a valve, the erroneous diagnosis of chronic aortic regurgitation on the basis of a diastolic murmur will be proportionately less common than that of mitral stenosis. The aortic diastolic murmur in cases with subacute bacterial endocarditis, as noted above, is a quite reliable indication that vegetations are present on the aortic valve.

Part II—Prognosis and Therapy

Of the 250 cases studied, 246 could be adequately followed up. None of these survived long, but in one instance there was a cessation of findings referable to subacute bacterial endocarditis, and death was due to rheumatic myocarditis 13 months after the diagnosis of bacterial endocarditis had been made. In this series of cases, this patient, who had received no specific therapy, was the sole instance of apparent recovery, but it is possible that he should not have been included in the series at all; thus the only possible recovery of the entire lot was himself, a somewhat doubtful case to start with. His record follows:

B. Di N. was found to have heart disease at the age of 17, six months before his first admission to the Massachusetts General Hospital (on March 19, 1928) with the chief complaint of shortness of breath on slight exertion. The diagnosis of rheumatic fever was made, with mitral stenosis and regurgitation and aortic regurgitation: the presence of adherent pericardium was suspected. After discharge, he remained in bed for six weeks, in bed and chair for 14 months, and was then up and about and capable of moderate exertion while receiving digitalis, despite signs of rheumatic activity from time to time.

Three days before his second hospital admission (on October 27, 1930) he became aware of sudden, severe palpitation, and had slight fever and cough. The

* It is possible that in one of these cases, one with a patent ductus arteriosus and slight coarctation of the aorta already mentioned, vegetations on the aortic valve gave rise to a diastolic murmur which was obscured by that resulting from patency of the ductus. Vegetations on the aortic valve, like those on the mitral, were implanted in this instance upon a valve apparently normal previously.

electrocardiogram showed auricular fibrillation. Two of four blood cultures were positive for *Streptococcus viridans;* there were repeated crops of petechiae, a splinter hemorrhage, low-grade fever to 100.8° F. by rectum, splenomegaly, 1–2 red blood cells per high power field in the urine, but no anemia or clubbing of the fingers. The diagnosis of subacute bacterial endocarditis was made. The patient was discharged November 20, 1930 to the Beth Israel Hospital, where he gained weight, had no rise in temperature over 99° F. by mouth, and showed no further petechiae. All six blood cultures taken there showed no growth. He did have three attacks of sharp left upper quadrant pain, however, which suggested splenic infarction.

At home, on a restricted régime, the patient had no complaints until four weeks before his third admission to the Massachusetts General Hospital (on June 24, 1931) when he suffered from epigastric pain, nausea, vomiting, dyspnea, cough, and nocturia. On admission he was dyspneic and showed mild icterus, slight cyanosis, and a definite Broadbent's sign, but no petechiae or fever. Two blood cultures were negative. The urine showed a few red blood cells, a slight to a large trace of albumin, and a few granular and hyaline casts. Blood non-protein nitrogen was 42 mg. per cent. After returning home, the patient suffered from dyspnea, palpitation and nervousness, and six weeks before his fourth admission (on November 19, 1931) he felt a severe constricting precordial pain lasting one hour. Two weeks before admission, he had great dyspnea, palpitation, and precordial pain. He coughed up blood-tinged sputum. The findings of tachycardia (difficult to control with digitalis), nervousness, weight loss, diarrhea, hot skin, stare, slight exophthalmos, and inability to shut his eyes suggested thyrotoxicosis; the basal metabolic rate was plus 26 per cent. There was no response to iodine, however, and the diagnosis was rejected. Aortic stenosis was now found to be present. Two blood cultures were negative; the urine showed a trace of albumin, and was loaded with hyaline and granular casts; the red blood count was 5,000,000. The patient died rather suddenly on December 10, 1931 in an attack of severe palpitation, tachycardia, cyanosis, and dyspnea.

At *postmortem examination,* the heart weighed 875 grams, and showed acute and chronic rheumatic endocarditis of the mitral, aortic, and tricuspid valves, with mitral and aortic stenosis and insufficiency and tricuspid insufficiency. The myocardium contained Aschoff bodies. There was a thick yellowish nodule 3–4 mm. in diameter on the sinus side of the right posterior aortic cusp, and a "deposit of relatively thick grayish nodules along the line of closure of the tricuspid valve." These nodules were not sectioned, but the latter nodules appeared identical with nodules studding the pericardium, which on microscopic examination showed dense hyaline material. The spleen was greatly enlarged, weighing 310 grams. There was chronic adhesive pericarditis, with fibrous pleuritis, and general chronic passive congestion. The kidneys showed moderate fibrous intimal thickening of the arterioles, and, rather uniformly throughout, some hyalinization of glomerular tufts, proliferation of the endothelial lining of glomerular capillaries, and moderate congestion. An occasional glomerulus showed capsular proliferation.

The diagnosis of subacute bacterial endocarditis here was made at the time of the second hospital admission on the basis of valvular heart disease, two positive blood cultures, petechiae, a splinter hemorrhage, splenomegaly, microscopic hematuria, and slight fever. From the time of discharge from this hospital stay until his death, a little more than one year later, the patient showed no further evidence of the disease. The finding at autopsy of firm nodules on the aortic and tricuspid valves is consistent with but not proof of the diagnosis of a healed bacterial endocarditis; these nodules were not studied microscopically, and may perhaps have contained bacteria. Such

a diagnosis, therefore, though indicated clinically, cannot be considered as certain pathologically; it is possible that the infection may have become only quiescent.* During the course of the review one other case seemed on superficial study to belong to the rare recoveries, but careful analysis forced its exclusion as an authentic instance of subacute bacterial endocarditis.

Intervals of normal temperature lasting as long as one week were common in the present series of cases, but afebrile periods of one month (after fever had once risen and the disease was clearly present) were rare; and no patient with this extended normal temperature, except the patient noted above, was free of signs and symptoms of the disease during so long a period of time.

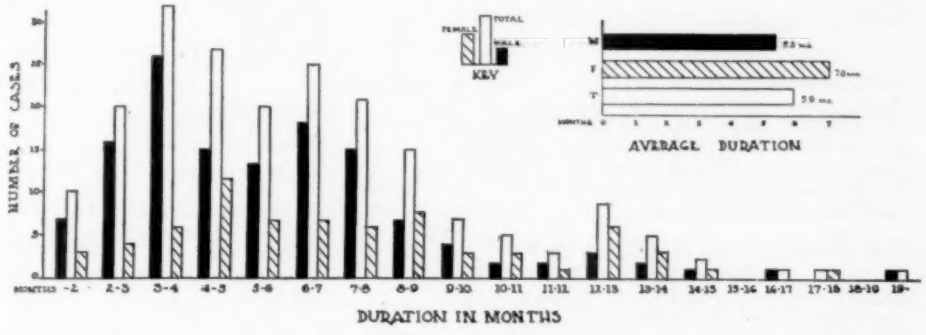

CHART 5. The duration of infection in subacute bacterial (streptococcal) endocarditis.

Uncertainty as to the time of the onset makes difficult a determination of the length of the infection, for in many instances the disease at first pursues a very mild course. In as far as possible, the duration has been reckoned from the onset of malaise. Chart 5 shows the average duration for males and females and for the whole group, and apportions the cases according to the number of months of survival. The numerically largest group survived three to four months, the second largest four to five months. The longest duration of infection in any instance was 19 months. The distinct difference in the duration in females, with an average of seven months, from that of males, with an average of 5.3 months, is puzzling. The younger average age of the female victims (25.7 years) as compared with the average age of the males (35.2 years) may be a factor in this discrepancy.

Treatment, 1927–1939. In few, if any, other diseases have such a number and diversity of treatments been attempted as in subacute bacterial endocarditis. These various methods, with the number of instances of their use, are recorded in table 2. Except for the newer chemotherapeutic drugs,

* Particularly the splenomegaly and renal changes found at autopsy raise the possibility here of the "bacteria-free stage" of the disease, as described by Libman.[17] The lack of brown pigmentation of the face and especially the absence of anemia, among other features, make this interpretation very unlikely.

TABLE II

Forms of Therapy Used in Subacute Bacterial (Streptococcal) Endocarditis; Study of 250 Patients Treated January 1927—March 1939

BIOLOGICAL

Transfusions

Whole Blood Transfusions	45 Patients
From Immunized Donors	3
From "Recovered" Patient	1

Bacteriophage

Alone	7
In Combination with Acriflavine	1

Vaccines

Autogenous	9
Stock	2
B.C.G.	1

Sera

Streptococcus Lysate (Lilly)	1
Antistreptococcal Serum (Parke-Davis)	1
Polyvalent Antistreptococcal Serum	1
Scarlet Fever Streptococcal Antitoxin	1
Antistreptococcal Horse Serum (Foshay)	2
Antistreptococcal Goat Serum (Foshay)	1
Antimeningococcal Serum	1

Inoculation with Living Organisms

Str. viridans from the Patient's Blood	5
Malaria—Injections of Infected Blood	1
Rat-Bite Fever—Injection of Blood from Guinea-Pig Infected with *Spirocheta morsus-muris*	1

DRUG

Chemotherapeutic

Sulfarsonal	1
Phenyl Mercuric Nitrate	2
Quinine Compound	1
Bismuth Tartrate	1
Neoarsphenamine	2
Sodium Cacodylate	4
Carbolic Acid	1
Metaphen	2
Acriflavine	2
Gentian Violet	3
Mercurochrome	3
Prontosil	5
Sulfanilamide	24
Sulfapyridine	4

Non-specific

Peptone Solution (i.v.)	1
Sterile Milk (i.m.)	2
Turpentine (i.m.)	2

Miscellaneous

Sodium Nucleinate	1
Spleen Marrow	1
Cysteine	1
Salyrgan	1

PHYSICAL

Hyperthermia	1
Ultraviolet Radiation	2
Radiotherapy over Heart	3
Sunlamp	4

SURGICAL

Attempt to Obliterate Infected Patent Ductus Arteriosus	1
Cautery of Deep Fascia of Chest Wall	1
Tonsillectomy (Attempt to Remove "Focus of Infection")	4
Tooth Extraction (Attempt to Remove "Focus of Infection")	14

SYMPTOMATIC AND GENERAL

This includes the administration of opiates, iron, salicylates, digitalis, high caloric diets, vitamins, etc.	Many

these agents produced only slight temporary improvement, or, far oftener, none at all. Frequently they increased discomfort and hastened death; chills, heightened fever, nausea, vomiting, burns, abscesses, deafness, and prostration were among their toxic effects. In some instances, transfusions of whole blood helped, particularly in patients with severe anemia. Immunotransfusions were not superior. After the withdrawal of 1000 c.c. of blood from one of the three patients treated by this method,[18] she was given a single transfusion of 1800 c.c. of blood from three donors immunized with killed

cultures of her organisms. In the next 15 weeks she received five more 500 c.c. immunotransfusions, but the treatment did not change the course of the disease. Agglutination tests on the blood of the patient and donors showed that the patient possessed a higher titer of antibodies than any of the donors. Many investigators [19, 20, 21] have demonstrated the almost constant presence of antibodies, both agglutinins and complement-fixing bodies, for the patient's own and homologous organisms, in the blood of those with bacterial endocarditis.* The occurrence of this antibacterial power in the patient's own blood points to the futility of biological and non-specific drug therapy intended to add to or to stimulate the production of immune bodies in the blood. These considerations apply strongly to the transfusion of blood from donors recovered from *Streptococcus viridans* infections, a measure which the many frantic and pathetic appeals by radio and newspaper have publicized as the sole chance for sufferers from subacute bacterial endocarditis. Besides raising hope falsely in the families of these patients, such appeals render them prey to very dubious "recovered" donors, led more by financial than humanitarian desires.[23]

The one patient who received an injection of guinea-pig blood infected with the *Spirocheta morsus-muris* developed symptoms of rat-bite fever so alarming that specific therapy had to be administered against this disease, but when it had been controlled, the bacterial endocarditis remained.

In one instance, a bold surgical treatment was attempted, the ligation of an infected patent ductus arteriosus. Because of strong adhesions between the ductus and the right pulmonary artery, successful closure was impossible. The patient died four days later, and autopsy showed vegetations at the pulmonary orifice of the ductus, and growing extensively on the wall of the pulmonary artery below. In a report of this case,[24] the authors stated their belief that such therapy can succeed only when vegetations are confined to the ductus and its immediate vicinity; they found in the literature, however, only a single instance in which these were limited to the pulmonary orifice of the ductus, and only a few in which the lesions were restricted to the ductus and the pulmonary artery. Despite this earlier failure, Touroff, guided by the pioneer work of Gross [25] in ligating the non-infected ductus, was able to report in 1940 the surgical closure of an infected patent ductus arteriosus, with recovery from subacute bacterial endarteritis.[26] This operation, also performed early and with success by Keele in England in a case of influenzal endarteritis,[27] has resulted in numerous apparent cures reported by several workers.†

* Poston and Orgain,[22] however, could demonstrate "no significant serologic evidence of immunity" "in the active bacteremic stage of bacterial endocarditis" among eight patients, five of whom were infected with *S. viridans*. In some of these patients, immune bodies appeared or increased with the disappearance of bacteremia.

† Touroff [28] believes that surgical closure of the patent ductus arteriosus overcomes the infection by (*a*) preventing the entrance into the aorta of infective material arising from the pulmonic side of the ligature, and allowing it to pass only into the pulmonary artery, (*b*) preventing traumatization of vegetations within the ductus and pulmonary artery by the strong aortic current, thus reducing the amount of infective material swept into the pul-

Removal of tonsils and teeth, even though heavily infected, proved futile. With the bacteria implanted in the endocardial vegetations, it is hard to imagine how removing such foci, even though they may have been the original source of infection, can cure. One of us (S. R. K.) [33] has seen a second attack of subacute bacterial endocarditis follow directly the extraction of two abscessed teeth, in a patient apparently cured by one of the newer methods of therapy (sulfapyridine and heparin); the importance of eradicating foci of possible reinfection *before* beginning treatment has therefore been stressed. The most imaginative method of treatment noted was perhaps the use of salyrgan, "to dehydrate the patient to render the environment less favorable to the organisms." Although no patients underwent therapeutic splenectomy, it is interesting to note that the disease occurred and followed its usual course in one patient whose spleen had been removed five years earlier because of Gaucher's disease.

Of the general methods of therapy, the use of large doses of vitamin C has particular significance, in view of the importance of this vitamin for effective wound healing [34, 35] and the demonstration of its deficiency in patients with prolonged infections.[36]

The use of specific drug therapy showed no noteworthy effect on the course of the disease prior to the introduction of the sulfonamides. No definite improvement was observed in the five patients who received Prontosil, but the use of sulfanilamide in 24 cases was followed by lowered temperatures in five patients and by negative blood cultures in two. Among the four cases in which sulfapyridine was used, it appeared more effective than sulfanilamide in reducing the temperature; two patients showed negative cultures for a time, but none derived prolonged benefit. Despite the failures of these new drugs to eradicate the infection, they had done more—in tempering the fever and even in ridding the blood stream of streptococci, if only briefly—than any of the variegated measures had accomplished against this disease through the years. By doing so, they raised the hope

monary circuit, and (*c*) cutting off this aortic current which acts to dilate the pulmonary artery and its branches and to drive the organisms through, thereby aiding the lung capillaries to filter out the organisms. Libman [29] believes that recovery is influenced largely by the cutting off of the supply of arterial blood to the organisms on the pulmonic side of the closure and the decreasing of tension within the pulmonary artery.

In the ligated non-infected ductus, these same factors, we should believe, would tend to avoid or abort later infection. Surgical closure also would block the aortic current from roughening further the endothelium of the pulmonary artery and pulmonic end of the ductus, and from causing turbulence in them, both of which favor bacterial implantation. Persisting irregularities already present there, however, might serve as a nidus of infection, as might the ostium or cul-de-sac at the aortic end of the ductus. Gross [30] stresses that ligation often fails to obliterate the ductus completely, and that the remaining tiny opening may permit swirling into the pulmonary artery favorable to implantation; complete division would eliminate this factor. Of 81 successfully-operated-upon non-infected cases reviewed by Shapiro and Keys,[31] two [30, 32] later developed subacute bacterial endarteritis. In one, the ductus had previously re-canalized: such an event (believed to have occurred in 14 of the 81 cases) would negate any value in avoiding infection. More extensive and accurate data as to the incidence of infection in the untreated patent ductus, and long observation of the surgically-treated non-infected cases, are needed to judge the worth of the operation as a preventative of bacterial endarteritis.

that the day of successful treatment of subacute bacterial endocarditis might not be far distant.

Summary and Conclusions

1. A series of 250 well-substantiated cases of subacute bacterial (streptococcal) endocarditis studied in five Boston hospitals and in private practice from January 1927 to March 1939 has been analyzed for three purposes: (*a*) to evaluate more completely the clinical picture; (*b*) to establish a baseline of prognosis, especially as a means by which the effects of therapy can be measured; and (*c*) to determine the results of treatment prior to the intensive use of the newer chemotherapeutic drugs and the anticoagulants. All the patients had cultures positive for nonhemolytic streptococci of the alpha (viridans) or, rarely, the gamma (anhemolytic) variety. In these clinically definite cases, with two or more positive blood cultures as a rule, the ratio of positive cultures to all cultures taken was 74.4 per cent, being 66.8 per cent from 1927 through 1932 and 78.8 per cent from 1933 through 1938.

2. The male sex was preponderant in the ratio of about 2 to 1 (161 to 89, or 64.4 per cent to 35.6 per cent).

3. The average age of the entire group was 31.8 years, with a range from 2½ to 78. The majority of the cases were in the third and fourth decades, the former predominating with 80 patients. The average age of females (25.7 years) was distinctly less than that of males (35.2 years).

4. The great majority of the 250 cases had rheumatic heart disease (224 or 89.6 per cent—though the rare possibility of a previously unimpaired heart could not be completely excluded in some of those who were not autopsied; in two of 57 autopsied cases, hearts believed clinically to show rheumatic [mitral] disease presented no apparent preëxisting lesions).* Mitral valve involvement alone (usually regurgitation) was diagnosed in 96 (42.9 per cent of the rheumatic group). Aortic valve involvement was diagnosed in 130 cases (58.0 per cent of the rheumatic group), divided into two cases of stenosis, 106 of regurgitation, and 22 of stenosis and regurgitation. Of these 106 cases, 74 also had mitral diastolic murmurs, which may or may not have denoted mitral stenosis †—or even prior rheumatic mitral disease; the apical systolic murmur present in most of the group was likewise not necessarily diagnostic of organic mitral disease, and for this reason it is not possible to break down the group into uncomplicated aortic and combined aortic and mitral lesions. Congenital defects were diagnosed in 13 patients or 5.2 per cent of the 250 cases, including five instances of patency of the ductus arteriosus and five cases of ventricular septal defect.

5. The most common predisposing cause of the illness in the cases studied, if we exclude the indefinite condition called grippe—which may

* These two cases are excluded from the rheumatic group but left in the sub-group *diagnosed* as mitral valve involvement, thus giving 226 (100.9 per cent) for a total of the component sub-groups, rather than 224 cases.

† See P. 58, No. 9.

have been the early stage of the disease itself—was some dental procedure, especially extraction. Exact figures are not possible in this series, for often no statement about previous dental treatment was included in the history, but it is estimated that almost one in four cases of subacute bacterial endocarditis gives such a history if inquiry is made. It has been stressed that individuals susceptible to this disease should be particularly attentive to the care of their teeth and should avoid harsh dentistry and extractions not clearly indicated.

6. The incidence of salient clinical findings in this group of 250 cases was as follows: heart murmurs in 99.2 per cent, petechial hemorrhages in 86.5 per cent, palpable spleen in 59.0 per cent, hematuria in 49.0 per cent, clubbed fingers in 46.7 per cent, and chills in 40.5 per cent. It was not the rule to find all these conditions present in the same patient; for example, splenomegaly, clubbing, and petechiae were present together in only 13.1 per cent, and none of these three significant findings in as many as 6.1 per cent.

7. The differential diagnosis of subacute bacterial (streptococcal) endocarditis includes a consideration of many different diseases. Those more commonly considered in the present series of cases were "grippe," rheumatic fever, renal calculus, meningitis, pleurisy, tuberculosis, pneumonia, subarachnoid and cerebral hemorrhage, brain tumor and abscess, central nervous system and latent syphilis, and angina pectoris. Among those less commonly considered, there were acute appendicitis, neurosis, undulant, typhoid, and typhus fevers, perinephric and subphrenic abscess, and portal thrombophlebitis. The commoner manifestations of the disease, namely, fever, local symptoms from embolism to the brain or spleen or other viscera, and renal involvement, were the reason for this wide diversity of suspected diseases. It has been emphasized that fever and malaise in a patient with a heart murmur may mean subacute bacterial endocarditis, and, unless another cause is clearly recognized, it is important to confirm or exclude the diagnosis by repeated blood cultures.

8. Analysis of this series revealed instances of the concurrence of rheumatic fever and subacute bacterial endocarditis. It appears that the latter disease may serve as a factor to activate rheumatic fever in susceptible individuals, and also that bacterial endocarditis may arise during the course of rheumatic infection.

9. Chronic rheumatic mitral stenosis was too often diagnosed in the presence of a mitral diastolic murmur, which in a number of cases that came to autopsy was apparently the result of dilatation of the left ventricle or of vegetations on the mitral valve; only three of 19 cases, 10 with and nine without aortic regurgitation, diagnosed as having mitral stenosis during life, showed such stenosis at autopsy.

10. Of the 250 cases of subacute bacterial (streptococcal) endocarditis studied, 246 were adequately followed up and all died of the disease except one who succumbed to rheumatic myocarditis after a period of one year of freedom from evidence of bacterial endocarditis.

11. The duration of the disease to death averaged 5.9 months, with longer duration for females (7.0 months) than for males (5.3 months). The numerically largest group survived three to four months, the second largest four to five months. The longest survivor lived 19 months. An appreciable number—18—lived more than a year.

12. No therapy was curative. Occasionally there seemed to be a temporary effect on the disease from some of the measures tried, but it must be remembered that the disease itself has a markedly variable course. Therapy included whole blood transfusions in 45 patients, and transfusions from immunized donors in three cases and from a "recovered" patient in one, bacteriophage in eight, autogenous vaccines in nine cases, stock vaccines in two, antistreptococcal serum of various kinds in seven and inoculation with living organisms from the patient's blood in five. Injections intramuscularly of sterile milk and of turpentine were administered in two cases each, and hyperthermia, radiotherapy, and ultraviolet radiation in a few scattered instances. Various chemicals were used, including sodium cacodylate in four, neoarsphenamine in two, metaphen in two, acriflavine in two, gentian violet in three, mercurochrome in three, and in the early days of sulfonamide therapy, Prontosil in five, sulfanilamide in 24, and sulfapyridine in four. Use of this last group of drugs was followed in some cases by reduced fever and negative blood cultures, neither of which persisted.

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NOTES ON THE TREATMENT OF SUBACUTE BACTERIAL ENDOCARDITIS ENCOUNTERED IN 88 CASES AT THE MASSACHUSETTS GENERAL HOSPITAL DURING THE SIX YEAR PERIOD 1939 TO 1944 (INCLUSIVE) *

By Paul D. White, M.D., *Boston, Massachusetts,* Marion W. Mathews, M.D., *Augusta, Georgia,* and Elwyn Evans, M.D., *Winter Park, Florida*

In this note we shall report the findings in the 88 clearcut cases of subacute bacterial endocarditis which were treated at the Massachusetts General Hospital for the nearly-six years from the beginning of 1939, which terminated the period of 12 years covered in the analysis of Kelson and White [1] presented above and began a period of special chemotherapy (January 1939–November 1944 inclusive). The first seven cases were reported by Kelson and White in 1939.[2] Thirty-eight more of these 88 cases were reported by Leach et al. in 1941.[3] Forty-three new cases have been treated since. Our criteria for a clearcut case have been the usual clinical findings backed by three positive blood cultures or confirmation at autopsy. There were two recoveries in the first seven cases reported by Kelson and White in 1939; one of these is still alive and well; the other died later of acute rheumatic heart disease.

Forty-nine (55.8 per cent) of the 88 cases were males. The ages varied from 14 to 70 years with an average age of 31.8 years. All patients had heart murmurs. A diagnosis of chronic rheumatic heart disease was made in 76 cases, and the classification as to valves involved in order of frequency was: mitral, mitral and aortic, and aortic alone. Congenital lesions were found in 12 cases with the following frequency: patent ductus arteriosus six times, bicuspid aortic valve alone twice, interventricular septal defect alone twice, bicuspid aortic valve and interventricular septal defect with vegetations on both lesions once, and interventricular septal defect plus rheumatic heart disease with aortic stenosis and insufficiency, vegetations being found at necropsy on both defects, once.

Bacteriology

The diagnosis was established bacteriologically ante mortem in 83 cases (94.3 per cent) and by autopsy in the remaining five. All of the 83 had at least three positive blood cultures, and the majority had more. The alpha

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hemolytic streptococcus was the offending organism in all the 88 cases, except 12, in which the *Staphylococcus albus* was the causative organism in two, the nonhemolytic streptococcus in six, *H. influenzae* in two, the nonhemolytic *Streptococcus fecalis* in one, and the beta hemolytic streptococcus in one. In the five cases confirmed by postmortem examination the bacterial findings ante mortem were as follows: two had two positive cultures for alpha hemolytic streptococci and three had consistently negative cultures. One of these had 15 negative cultures, but at necropsy type 13 pneumococci were obtained from the heart's blood. Alpha hemolytic streptococci were found post mortem in the heart's blood in three of the remaining four cases and were grown from the heart valves in the other.

Treatment

All of the patients were given high vitamin high caloric diets, and most of them supplementary iron and vitamin concentrates. Transfusions and other supportive measures were carried out as indicated. Forty-five received sulfonamides alone; 32 received additional therapy as well; two had no treatment other than general measures; and since January 1944 nine have been given penicillin, some with and some without sulfonamides. Six of the patients, treated with sulfonamides only, received grossly inadequate therapy for one reason or another (five patients received one or two days of medication only and the other, four days of treatment terminally). Until the latter part of 1941 sulfonamide therapy was most frequently initiated with sulfapyridine, changing sequentially to sulfathiazole or sulfanilamide, depending on the response of the patient. However, after that time sulfadiazine became the starting drug of choice. Of the 32 who received additional therapy in the form of a single preparation or of combinations, 17 received heparin (11 for five days or less, one for seven days, and five for 10 to 23 days), six intravenous typhoid vaccine, four sodium paranitrobenzoate, two neoarsphenamine, and five of the more recent ones, dicoumarin which is now replacing heparin in the therapy of some of our cases. One of the patients who had less than five days of heparin therapy received inadequate sulfonamide therapy as well (three days' treatment terminally). Heparin was given in such a quantity as to keep the clotting time at approximately one hour. Twenty cubic centimeters given in isotonic saline or glucose in 24 hours usually sufficed. Dicoumarin was given in an average dose of from 100 to 200 mg. per day in order to maintain a prothrombin time of 40 to 60 seconds. The normal prothrombin time was determined against a control which usually varied from 18 to 22 seconds. Four of the patients, after a rather prolonged trial on chemotherapy, were given hyperthermia by means of a fever cabinet, without obvious beneficial effect. This treatment was kindly carried out for us by Dr. John Gibson of the Peter Bent Brigham Hospital.

Results from Sulfonamide Therapy

Of the 77 patients who received sulfonamide therapy, including the six who received grossly inadequate amounts, 66 died, five recovered, follow-up information was not obtained on five, and one was still living but was not in good health three and one-half years after leaving the hospital (Case 6). This patient has not been included in the list of recovered cases despite the facts that she had been reasonably well without medication for more than three years and that three blood cultures had been negative, because we have not ourselves been able to see her during the last 1½ years; this very duration of life, namely 3½ years since the original illness, does of course strongly point to recovery from the subacute bacterial endocarditis; a recent report from her doctor states that she is now having a "recurrence of rheumatic fever." Three of the recovered patients have been well for two, three, and five years although one is now convalescing from active rheumatic fever. The other two "cures" were proved at autopsy, one patient dying from an unrelated accident, and the other from acute rheumatic fever. One of the patients who recovered received four days of heparin therapy which was thought not to have altered the course of the disease. Blood cultures became negative and rectal temperatures were reduced to 98.6° to 100° F. during sulfonamide therapy before heparin was started on another patient who recovered. One of the remaining 15 patients who received heparin (seven of whom received five days or less of medication) recovered, but none of the other patients who were given additional treatment survived. Thus, five (6.5 per cent) of the 77 patients who received sulfonamides recovered, and one remains unclassified as yet.

Fifty-two of the 77 sulfonamide-treated patients showed a definite partial to complete loss of fever within one to three days after treatment was instituted, the afebrile state lasting from two to 12 days. One patient who received typhoid in addition to sulfonamides had normal temperature consistently between episodes of artificially induced fever. Subsequently, various degrees of fever returned in the patients who died, despite continued medication. The other 24 patients showed little or no response to the drugs. Sulfapyridine appeared to have a greater antipyretic effect than the other sulfonamides.

One of the two patients in whom the *Staphylococcus albus* was the causative organism recovered.

The following are summaries of the cases in which recovery occurred.

Case Reports

Case 1 (previously reported[1]). E. S., a 21 year old man, was admitted to the hospital in April 1939 because of fatigue, anorexia, fever, headaches, and chilly sensations of four days' duration. He had had rheumatic fever at the ages of 10, 11, and 13 years. Three blood cultures taken before admission were positive for *Streptococcus viridans*. He appeared poorly nourished and chronically ill. Systolic and diastolic murmurs were present at the aortic and mitral areas. His temperature was

104.6° F. rectally. He was given 6 grams of sulfapyridine daily and on the second day his temperature dropped to 101° F. rectally. He complained of joint pains and his electrocardiogram showed partial auriculoventricular block. Eight days later heparin was started and was continued for two weeks. During this time the rectal temperature dropped to 99 to 100° F. Sulfapyridine was continued for two more weeks. A few weeks later auricular fibrillation occurred. Slight fever persisted, but it was thought that the subacute bacterial endocarditis was arrested and that he now had active rheumatic fever. Nineteen consecutive blood cultures were negative. He died in congestive failure four months later when postmortem examination revealed evidence of acute and chronic rheumatic heart disease and healed, calcified vegetations of bacterial endocarditis on the mitral valve. Ground fragments of these vegetations showed no growth on culture and microscopic examination of the involved valve and vegetations showed no bacteria.

Case 2 (reported previously [1]). A. C., a 23 year old woman, was admitted to the hospital in April 1939 because of chilly sensations, fever, malaise and joint pains for five months. She had had rheumatic fever at 10 years of age. A blood culture taken three months before admission was positive for alpha hemolytic streptococci. She appeared undernourished and pale. Systolic murmurs were heard in the aortic and mitral areas and several petechiae were found. Two further blood cultures were positive, so sulfapyridine was started on the seventh hospital day. Blood cultures became negative and rectal temperatures ranged from 98.6° to 100° F. Heparin was started on the seventeenth day and continued through the thirty-fourth day. Sulfapyridine was continued for eight more days. Blood cultures were negative and the patient remained in excellent health without medication until December, 1943 when she had a "cold" and following that began to lose weight and noticed that she became more easily fatigued. In September, 1944 she had to be readmitted with a diagnosis of active rheumatic fever. Eight days before admission she had nosebleeds and hot flashes with a "cold." Blood cultures during hospitalization were negative and there was no evidence of subacute bacterial endocarditis. She was dismissed on October 20, 1944 to remain in bed at home and when last seen, December 1, she was convalescing satisfactorily from her acute rheumatic infection.

Case 3 (previously reported [2]). W. N., a 21 year old male with a patent ductus arteriosus, who had been told five months previously that he had a streptococcic infection in his blood, was admitted in June 1940. He was thin and appeared chronically ill. Four out of five blood cultures were positive for alpha hemolytic streptococci. The fever responded immediately to sulfapyridine, rose to 103° F. 10 days later, and returned to normal by the fifteenth day. On the seventeenth day heparin was started and continued for four days when the temperature increased to 102.5° F. and a macular rash appeared. All medication was then stopped. The rash recurred every time sulfapyridine was resumed and so sulfathiazole was tried. After seven days of this treatment, an erythema nodosa-like rash appeared which subsided along with the fever three days after the dose was reduced from six to three grams daily. This dose was continued for six more months. In March 1941 the patent ductus was ligated by Dr. Robert Gross who could palpate no vegetations of subacute bacterial endocarditis. While in excellent health the patient was killed in an automobile accident in July 1941. Autopsy revealed a few small, slightly raised areas in the pulmonary artery close to the mouth of the ductus arteriosus and on the pulmonary aspects of the pulmonary valve cusps without evidence of inflammation or vegetations.

Case 4. M. R., a 33 year old female who had chronic rheumatic aortic and mitral stenosis and insufficiency, entered the hospital in November 1941, with a history of having had a sore toe for three days and chills and fever for three months. Her temperature on admission was 102.8° F., and the first three blood cultures were positive

for alpha hemolytic streptococci. There was an immediate and permanent disappearance of the fever with sulfadiazine, and no positive blood cultures were obtained after treatment was instituted. She was discharged improved on December 18, 1941 on a four gram daily dose of sulfadiazine which was continued until May 20, 1942. Since then to date she has remained well without medication.

Case 5. G. B., an 18 year old girl with chronic rheumatic aortic and mitral stenosis and insufficiency, was admitted on January 10, 1942 with a history of having had numerous red spots on her legs seven months previously. After that time she had daily fever, sensations of pressure in the precordium, fatigue, anorexia, and weight loss. The highest known temperature was 102° F. On physical examination the lower pole of the spleen was found to be four fingers below the left costal margin. Five of 10 blood cultures were positive for *Staphylococcus albus.* There was an immediate partial response of the fever during the first four days of sulfathiazole therapy, followed by complete and permanent reduction of the fever and persistently negative blood cultures. She was perfectly well when last seen in the Cardiac Clinic on June 14, 1944. The spleen was no longer palpable.

Case 6. E. A., a 23 year old woman, was admitted to the hospital in February 1941 because of pain in her left upper abdominal quadrant, sore finger tips, and red painful areas on her legs during the preceding six weeks. Physical examination revealed a pale, well developed woman. The heart was slightly enlarged and systolic and diastolic murmurs were heard in the mitral area. Several petechiae were seen. During the hospital stay embolic phenomena were observed and three blood cultures were positive for alpha hemolytic streptococci. There was almost a complete response of her fever to sulfapyridine for five days, but by the eighth day her temperature was 104° F. and she had developed generalized lymphadenopathy and an erythematous rash. Her temperature returned to normal the next day after stopping the drug. Marked systemic reactions occurred after resuming sulfonamides on two later occasions. During the first seven weeks after her discharge from the hospital on April 23, 1941, without medication, she noticed painful finger tips on two occasions. Blood cultures remained negative, however. A molar tooth was extracted on September 23, 1941 at which time she took sulfadiazine for four days without deleterious effect. A blood culture was negative at this time. She was not seen again until May 1943, when physical examination revealed evidence of infection (fever, leukocytosis, and a rapid sedimentation rate), anemia, cardiac murmurs as before, and an enlarged spleen. One blood culture was negative. She stated that she had not had fever or petechiae in the interim of one and one-half years, but we could not be certain that this statement was correct since she did not think she had fever when we examined her.

She was not gotten in touch with again until December 11, 1944 when her local physician stated that she had been well except for occasional episodes of acute rheumatic fever. He saw her on December 11 because of joint pains and swelling which began on December 10 and he thought that she again had rheumatic fever.

During the same period, four patients who probably had subacute bacterial endocarditis but did not fulfill our criteria for clearcut cases were treated in the hospital. All showed evidence of the infection superimposed on chronic rheumatic valvular involvement or congenital heart disease. Two had two positive blood cultures each for alpha hemolytic streptococci and the other two had one positive culture each. One patient received inadequate therapy and two no treatment. Three of the patients died and one recovered.

The following is a history of the patient who recovered.

W. E., a 38 year old male with chronic rheumatic aortic and mitral valve disease, was admitted in April 1941 with a history of having had influenza five months previously, trouble with his joints for four months, malaise, and fever. While in the hospital he had definite evidence of emboli and one of three blood cultures was positive for alpha hemolytic streptococci. There was an immediate favorable response to sulfathiazole which he took for 27 days, since when he has been perfectly well without medication.

Results from Penicillin Therapy

Since January 1944 when penicillin became available for use in small quantities, nine cases of subacute bacterial endocarditis have been treated at the Massachusetts General Hospital and Baker Memorial Hospital with penicillin, sometimes in combination with the sulfonamides, and the results have so far been encouraging although the follow-up period has been brief.*

Eight of the nine cases had rheumatic heart disease; the only clinically demonstrable lesion in five was mitral regurgitation; one had mitral stenosis and regurgitation with auricular fibrillation; one had aortic stenosis and probable mitral stenosis; and the eighth had both aortic and mitral regurgitation. There was one case of congenital heart disease with an interventricular septal defect. The group consisted of six females and three males whose ages ranged from 17 to 70 years. The alpha-hemolytic streptococcus was found in six cases, the non-hemolytic streptococcus in two cases, and the beta-hemolytic streptococcus in one case. The dosage of penicillin varied from 100,000 to 288,000 units daily for two to four weeks, the average case being given 200,000 units daily for three weeks. Three patients received sulfonamide before penicillin was given; one received penicillin with sulfonamides; one received penicillin alone during hospital treatment but was sent home on sulfadiazine; and four received penicillin alone.

To date (December 8, 1944) two patients have died, the first of cerebral embolism which occurred on the fourteenth day of treatment so that although there was a fall in temperature after penicillin was started, a normal level was never reached, and there was no way of evaluating therapy. The second died eight months after the completion of her course of penicillin, apparently from active rheumatic fever with cardiac failure complicated by

* Since this paper went to press four patients, three with rheumatic heart disease and one with congenital heart disease, have been admitted for treatment of subacute bacterial endocarditis, and three of these have to date (December 27) received penicillin. The first patient, a 27 year old man, received 2,280,000 units at another hospital; but after admission here on October 19, he had one culture positive for the alpha-hemolytic streptococcus and a splenic infarction so that a second course of therapy was begun on November 25. After three weeks of treatment he was sent home in excellent condition. The second patient, a 54 year old woman, continued to have low grade fever after the urinary infection for which she was admitted had subsided. Blood cultures showed *Staphylococcus albus*, and penicillin was started on December 1; to date (December 27) after three weeks' treatment she has become afebrile and feels much better. The third patient, a 56 year old man, whose blood cultures were positive for nonhemolytic streptococci, has become afebrile after three weeks' treatment. The fourth patient, an 18 year old boy with congenital heart disease, was given six weeks' intensive treatment with penicillin in another hospital; but since admission here, blood cultures have shown alpha-hemolytic streptococci, and he has had slight temperature elevation uncontrolled by sulfadiazine.

renal disease and possibly nutritional deficiency. Blood cultures were repeatedly negative, and she was bacteriologically "cured." Postmortem examination was not obtainable.

The remaining seven patients had a marked fall in temperature from one to four days after therapy was begun, and the temperature became normal within 9 to 27 days. Four of these seven cases are now apparently well, three being clinical and bacteriological "cures" approximately seven weeks, five months, and eight months after completion of one course of therapy; the fourth had a recurrence of the infection but is well two months after a second course of penicillin. This fourth patient was readmitted six weeks after discharge because of low grade fever and chest pain, and a blood culture taken on the day of admission showed nonhemolytic streptococci again; she was given a second three weeks' course of penicillin, and when she returned for examination on November 24, 1944 she was free of any evidence of infection. Of these four apparent "cures" one received penicillin alone; one had sulfonamides before penicillin was started; one had sulfadiazine during the last ten days of penicillin therapy, and after its completion; and the fourth case mentioned above who had a recurrence of the infection received sulfadiazine in the interim between the two courses of penicillin.

The fifth case of the seven survivors, a 58 year old woman, developed congestive failure during treatment and is now invalided by increasing dyspnea and edema for which she receives frequent injections of mercupurin; she has no clinical signs of subacute bacterial endocarditis, however, seven months after completion of therapy. There has been a question of recurrence in the remaining two cases, one of whom has returned for further therapy. This patient was readmitted six days after discharge with a chief complaint of upper abdominal pain, nausea, and vomiting. He had low grade fever and mild congestive failure but blood cultures were negative. There was in his case a question of the recurrence of rheumatic fever, but he was also given a second course of penicillin. His status was still uncertain three weeks after the completion of this treatment as he had just begun to have evening elevation of mouth temperature to 99.2 and 99.8 degrees accompanied by pain in his knee, calf, and instep. The last case of the seven survivors was apparently well for one month after the completion of his course of penicillin on November 4, 1944, but reported on December 9 that he had been having fever in the evenings of 99.5 to 100.8 degrees (by mouth) since December 6. He did not feel as well as usual although there was no joint pain, cough, or dyspnea.

Case 1. I. J. D. is a 23 year old white female who was admitted to the hospital December 20, 1943. She developed mitral stenosis and regurgitation after acute rheumatic fever at the age of 15, but had no symptoms until the age of 18 when she suffered from dyspnea and auricular fibrillation. She was maintained satisfactorily after that on digitalis and quinidine; she did secretarial work for a while, later married, and went through an apparently normal pregnancy. Her present illness began one month before her admission with an attack of the "flu" after which fever and

cough persisted. Blood cultures were found positive for the alpha hemolytic streptococcus, and she was given sulfadiazine for two and a half days and then sulfapyridine (6 gm. and then 4 gm. daily) for twelve and a half days. Her temperature fell to normal the third day after this medication was begun and remained normal for three days; it rose immediately after that and continued high although she remained on sulfapyridine. Penicillin therapy was begun on January 11, 1944, eight days after sulfonamide was stopped, 200,000 units being given either intravenously or intramuscularly every day for two weeks. There was an almost immediate fall of the temperature to a lower although not to a normal level for two days. During the following seven days the temperature rose again and stayed between 101° and 104°; after that it gradually fell to a lower level so that for the last two weeks of her hospital stay it ranged from 98.6° to 100.5° F. by rectum. The prognosis at the time of her dismissal on February 9, 1944 was unfavorable.

After her return home she failed to begin her temperature record until March 4, but it was normal then and remained normal or subnormal until the first part of April. Her blood cultures which became negative by January 31 remained negative and have continued to show no growth through September, 1944. She was symptom free after dismissal until she developed slight congestive failure during the early part of April; the congestive failure was followed by thrombophlebitis of the left leg, pulmonary infarction, and iliac phlebitis for which ligation of the inferior vena cava was done on April 13. Recovery from this was uneventful; the temperature remained normal and she continued symptom free except for some increasing congestive failure and another mild episode of thrombophlebitis on the right. On her last visit during August 1944 she was found to have marked edema of the face, sacrum, and both lower extremities. The exact cause of the edema was undetermined, although she responded to routine therapy in the hospital; several factors seemed to be responsible—cardiac failure, hypoproteinemia and renal failure, and she also probably had acute rheumatic fever. However, blood cultures which were taken repeatedly were negative. She was convalescing in the hospital and her condition was apparently satisfactory when she had cerebral embolism with left hemiparesis on September 24 and died on September 30.

Case 2. K. M. is a 27 year old white female who was admitted to the Baker Memorial January 15, 1944 with a chief complaint of epistaxis which had occurred daily for a week and which had lasted for nine or ten hours preceding admission. Her past history revealed a definite episode of rheumatic fever at the age of 11 after which she was told that she had a heart murmur. Her present illness began in November, 1943 during the sixth month of her second pregnancy with slight nonproductive cough, chilly sensations, malaise, anorexia, and fever so that she thought she had "grippe." In December the same symptoms recurred, and she had a temperature of 101° F. On January 5, 10 days before admission she had acute back pain which forced her to bed; later in the hospital this was considered due to acute sciatica or possible ruptured intervertebral disc. From November 1943 until January 15, 1944 she suffered from malaise, night sweats, and weakness, and thinks she probably had some low-grade fever although she continued to do her housework.

On January 21 she was delivered of a normal female infant which did well. After delivery her temperature was septic in type and rose to as high as 104.5° F. Sulfathiazole was given for eight days from January 30 through February 6 because of the possibility of pyelonephritis. Several blood cultures then became positive for nonhemolytic streptococci, and she showed petechiae. On February 21 she was transferred to the Massachusetts General Hospital where physical examination showed a heart of normal size with a short, harsh systolic murmur at the mitral area, a palpable spleen, and embolic phenomena. On February 19, sulfadiazine was started, six grams being given daily until February 29 without any apparent effect on the temperature which ranged from 100° to 104° F. Penicillin therapy was begun on

March 8, 200,000 units being given daily for 21 days by continuous intravenous drip. Her temperature dropped on the second day of treatment to a lower level and stayed between 100° and 101° F. with an occasional rise to 102° F. until March 30; then it fell to 99 and 100° F. by rectum and stayed within a normal range until April 12. On April 12 she had soreness of one wrist and a temperature elevation to 101° F. which responded to the administration of salicylates. By April 22 her temperature was again normal and it remained normal until her dismissal on May 13, 1944. Since that time she has been followed in the Cardiac Laboratory. Blood cultures which became negative by March 11 have remained negative through October 1944, and she has remained symptom free through October 1944 and gradually increasing her activity. She was apparently well when last seen on October 31, eight months after completion of the penicillin therapy.

Case 3. W. M. is a 38 year old white female who was admitted to the Massachusetts General Hospital on February 14, 1944, with the chief complaint of marked fatigability and night sweats which were noticed for the first time in October 1943 when she also had some palpitation and vague pains in her knees and shoulders. For ten days before admission she had chills every other night and questionable embolic phenomena appeared on one finger and on the internal malleolus. A diagnosis of rheumatic heart disease with aortic and mitral regurgitation had been made on a previous hospital admission although no history of rheumatic fever was elicited. After blood cultures became positive for alpha-hemolytic streptococci, intravenous penicillin therapy was begun on March 29, 200,000 units being given every twenty-four hours. There was an immediate fall in temperature to 100 degrees but a few days later there were elevations to 101 and 102 degrees. On April 11 she had a severe chill after penicillin was started, became comatose, and developed a left hemiplegia. Her temperature rose to 104 degrees and auricular fibrillation appeared. From that time her course was gradually downward until her death on April 19, 1944.

Case 4. E. J. is a 58 year old white female who was admitted to the Baker Memorial on April 11, 1944 with a history of pneumonia six weeks before. She was able to be up after the first three weeks of the illness but continued to have anorexia, weakness, and fatigue. On admission she was slightly disoriented, had high fever, a rapid heart rate with a loud systolic murmur at the apex, and numerous petechiae over her body; several blood cultures were positive for the alpha hemolytic streptococcus. Later she had emboli to her kidneys with hematuria and became comatose. She was given a total of 2,800,000 units of penicillin, approximately 100,000 units daily from April 20 through May 2. The temperature which had been fluctuating between 100° and 104° F. dropped to a slightly lower level by April 24, the fourth day of therapy, then fluctuated above normal until May 4 when it became normal. It remained normal until dismissal on June 3 except for slight rises on May 18 and June 1. Since dismissal she has been invalided by increasing congestive failure for which she has received digitalis in the hospital and at home since and has to be given mercupurin at five day intervals to relieve dyspnea, and edema. However, her family physician reported on November 21, 1944, that she had had no fever and no clinical manifestations of subacute bacterial endocarditis. No recent blood cultures have been obtained.

Case 5. A. C. is a 17 year old white female who was admitted to the Baker Memorial on June 2, 1944 because of slight left hemiparesis and fever which had a rather sudden onset two and one half weeks before admission. She had rheumatic fever at the age of 12 and following that developed aortic stenosis and possibly slight mitral stenosis. After cultures became positive for nonhemolytic streptococci, penicillin therapy was begun on June 6, a total of 6,600,000 units being given by continuous intravenous drip; at first 100,000 units were given daily and later 300,000 units a day, until July 7. Six grams of sulfadiazine were given daily with the penicillin from

June 1 to June 7, and one gram was given on June 8. Her temperature became normal on June 9 and 10 and remained within normal limits until June 16 when it rose to 100° F. On June 17 and 18 it was a little higher than normal and on June 19 it rose to 102° F. and fluctuated rather markedly from then until it returned to normal on July 3. On June 23 there was a temperature rise which was probably the result of a delayed transfusion reaction. On June 27 there was a rise to 103° F. which was probably due to a splenic infarction on June 26. From July 3 until July 23, rectal temperatures reached 100° F. daily but were usually lower than that and never higher. She was discharged on July 23 symptom free with negative blood cultures. There has been no fever since (to date, December 8, 1944).

Case 6. S. H. is a 17 year old white female with a known interventricular septal defect who was admitted on June 19, 1944 to the Baker Memorial with a chief complaint of fever. Her present illness began in March with a "cold" followed by pleurisy, cough, and fever. She was in bed for 10 days but then returned to school and was apparently well for about two weeks. However, in April she began having fever ranging from 100 to 101° F. which was highest in the evening and was accompanied by drenching sweats. In the hospital, cultures showed alpha hemolytic streptococci, and intravenous penicillin therapy was begun, 25,000 units being given on June 16, 100,000 units daily from June 17 through July 6, and 92,000 units on July 7. Her temperature became normal by June 18, and it remained at 99° F. or below until June 24. On June 25 and June 26 it was a little above 99° F. by rectum, and on June 27 it went to 100° F. After that, except for one rise slightly above 99 on July 11, it was normal until discharge. A culture taken on July 5 was negative and she became symptom-free. She was sent home on sulfadiazine grams 1½ daily. She did well for five weeks after dismissal but had to be readmitted on September 5 because of low grade fever which had been present for six nights. Two days before admission she had had pain in her right chest, made worse by coughing. A blood culture on the day of admission showed nonhemolytic streptococci and she was given another three weeks' course of penicillin. Since that time she has been symptom-free and afebrile. She returned for examination on November 24; at that time, two months after completion of her second course, no clinical evidence of infection was present, and blood cultures were negative.

Case 7. S. A. H. is a 70 year old white male who was admitted to the Massachusetts General Hospital on September 11, 1944 because he had been having chills and night sweats for the previous two to four weeks. He had not been feeling well since May although he had no specific complaints. His past history revealed a questionable episode of rheumatic fever at the age of 14 and a story of angina pectoris for the last five years. On physical examination there was a grade 2 to 3 mitral systolic murmur heard widely over the precordium but neither embolic phenomena nor splenomegaly were present. Three blood cultures showed the alpha-hemolytic streptococcus, and he was given 48,000 units of penicillin intramuscularly on September 21, then 192,000 units daily from September 22 through October 12, and finally 72,000 units on October 13th. His temperature fell to 99 degrees by rectum on September 21 and ranged between 98 and 100 degrees until the day after therapy was discontinued, when it rose again to slightly over 100 degrees and fluctuated between 99.5 and 100 until October 18 when it became normal. He was discharged on October 20, 1944, and felt quite well for three days. On the fourth day he began to have severe upper abdominal pains, anorexia, nausea and vomiting. He was, therefore, readmitted on October 26 and was found to be in very mild congestive failure. Blood cultures were repeatedly negative but his temperature ranged from below 98 up to 100 degrees by rectum. He was digitalized, and another three weeks' course of penicillin was begun on October 28. On November 8, after ten afebrile days, his temperature rose to 101 and 102 degrees and remained high until

November 12. After that until his dismissal on November 18, it was normal. Since that time he has been in a nursing home. He was fever-free there and asymptomatic until December 6 when he began to complain of severe burning sensations and cramping pains in his knee, thigh, and instep, and had a slight elevation of temperature to 99.2 and 99.8 degrees. His present status to date (December 8) is uncertain although it is thought that his recent illness has been due to active rheumatic fever, there being no evidence of a recurrence of the subacute bacterial endocarditis.

Case 8. J. L. is a 68 year old white male who was admitted to the Massachusetts General Hospital on September 13, 1944, with chief complaints of anorexia and constipation. He had stopped work four months before because of "dry heaves" and weakness, and after going to bed at home, developed constipation with occasional diarrhea. His past history was noncontributory. He denied having chills or fever but in the hospital his rectal temperature ranged from 99 to 102 degrees with an occasional rise to 103. On physical examination he appeared anemic and chronically ill but showed no positive findings otherwise except for a short, grade 2, systolic murmur at the mitral area. Several blood cultures were positive for alpha-hemolytic streptococcus, and penicillin therapy was started on September 26 and continued for 23 days, approximately 192,000 units being given daily through October 17. His course was uneventful after the first day of therapy, and his temperature did not go above 99 degrees by mouth or 100 degrees by rectum except on two occasions. Blood cultures taken on the second day of treatment were negative, and six others taken at intervals since then, the last on November 8, have also shown no growth. He was discharged on October 23 but has been seen since then on November 8 and December 6. He now appears well, is afebrile, and symptom-free.

Case 9. J. F. is a 33 year old white male who became ill with fever five weeks before admission to the Baker Memorial Hospital on October 5, 1944. He was known to have had a heart murmur at the age of five years and gave a rather questionable history of rheumatic fever in childhood. On the second day of his illness he was given sulfadiazine, and his fever began to subside. However, when the drug was discontinued five days later, his temperature rose to 103 degrees. It again subsided with sulfadiazine therapy, and although the drug was stopped it did not go above 102 degrees again but ranged usually between 100 and 101.5 degrees by mouth. A blood culture taken one week after the drug was discontinued was negative. On physical examination he showed a slightly enlarged heart with a grade 2 mitral systolic murmur and slight clubbing of his fingers. Four flasks of blood grew beta-hemolytic streptococci, and penicillin was started, 288,000 units being administered intramuscularly from October 15 through November 4, 1944. Before treatment was begun his mouth temperature ranged for the most part between 100 and 102 degrees. After the third day of treatment it did not go above 99 degrees, and after October 29 did not go above 98.6 degrees. A blood culture taken on October 25 was negative, and the patient was well for one month following the completion of penicillin therapy. On December 6 he began having low grade fever of 99.5 to 100.8 degrees (mouth temperatures) during the evenings, and when last seen on December 12 said that he felt under par. He had no joint pains, upper respiratory infection, cough or dyspnea. The physical findings were unchanged; his spleen was not palpable, and there were no petechiae. It was found that he had a recurrence of the infection and therefore he is receiving penicillin again.

Discussion

We have herewith briefly analyzed the series of 88 clearcut and four probable cases of subacute bacterial endocarditis treated at the Massachusetts

General Hospital from January 1939 to September 1944 inclusive, including the series of seven cases treated with sulfapyridine and heparin by Kelson and White in 1939, for comparison with the series of 250 cases studied in the Boston Hospitals from 1927 to 1939 and reported in the preceding paper by Kelson and White. Five (6.5 per cent) of 77 sulfonamide treated patients who were followed up recovered, and if two other patients who had valvular lesions, fever, embolic phenomena, and at least one positive culture are included, six (7.8 per cent) of 79 recovered. One patient who had been reasonably well without medication for over three years was not included among the list of cures to date because we could not be certain that she ever was cured. Recently she showed evidence of infection (fever, leukocytosis, and an elevated sedimentation rate) despite negative blood cultures. Four of the nine patients who were given penicillin are symptom-free and afebrile, seven weeks, two months, five months and eight months respectively after completion of therapy. One patient was free of infection for seven months after completion of treatment; she had many complications including iliac thrombosis and during the latter part of August severe congestive failure with probable active rheumatic fever. During convalescence from this episode she developed cerebral embolism on September 24 and died on September 30. One case died during treatment, and the other three are still ill, one with congestive heart failure, one with rheumatic fever, and one with recurrent bacterial endocarditis.

The opinion that the milder the infection and the earlier the treatment is instituted, the better the prognosis, is only partially confirmed. Most of the patients who did recover gave histories of several months' duration and showed definite evidence of the disease, whereas other patients with shorter histories of infection and milder symptoms failed to recover. It is possible that when certain bacteria are the causative organisms, the prognosis is better than when the *Streptococcus viridans* is the offending agent. One of our two patients who had positive cultures for *Staphylococcus albus* recovered. The transient antipyretic effect of sulfonamides, especially sulfapyridine, was noted. Fifty-two (68.8 per cent of the 77 sulfonamide treated cases) showed a definite partial to complete loss of fever within one to three days after treatment was instituted, the response lasting from two to 12 days. Sulfapyridine appeared to have a greater antipyretic effect than other sulfonamides.

Seventeen of the total series of 88 cases received heparin in the course of treatment; 11 for five days or less, one for seven days, and five for 10 to 23 days. Three of the five recovered cases had received heparin and two others had not. The unproved case of subacute bacterial endocarditis that recovered had received no heparin. Five of the total series received dicoumarin instead of heparin in addition to the sulfonamides. None of these cases did particularly well during therapy; three died in the hospital, and we have been unable to obtain information about the other two.

Four of the nine cases receiving massive doses of penicillin have remained

clear of evidence of bacterial endocarditis since treatment was stopped from two to eight months ago, but this is too short a time to draw any very definite conclusions; at least a year is needed for adequate follow-up but the results to date are more encouraging than from any other type of treatment. One case died of cerebral embolism during treatment and another from active rheumatic fever and congestive failure following cerebral embolism. The other three cases remain ill, apparently with congestive failure, rheumatic fever, and bacterial endocarditis respectively.

Summary

1. An analysis has been presented of a series of 88 clearcut and four probable cases of subacute bacterial endocarditis treated at the Massachusetts General Hospital from January 1939 to September 1944 inclusive.

2. Five (6.5 per cent) of 77 sulfonamide treated patients who were followed up recovered and quite possibly a sixth case (case 6), and if two other patients who had valvular lesions, fever, embolic phenomena, and at least one positive culture are included, six (7.8 per cent) or seven (8.9 per cent) of 79 recovered.

3. The opinion that the milder the infection and the earlier the treatment is instituted, the better the prognosis, is only partially confirmed.

4. The transient antipyretic effect of sulfonamides, especially sulfapyridine, was noted. Fifty-two (68.8 per cent) of the 77 sulfonamide treated cases showed a definite partial to complete loss of fever within one to three days after treatment was instituted, the response lasting from two to 12 days. Sulfapyridine appeared to have a greater antipyretic effect than other sulfonamides.

5. Seventeen cases of the sulfonamide series received heparin in the course of treatment; 11 for five days or less, one for seven days, and five for 10 to 23 days. Three of the five recovered cases had received heparin and the other two had not. Five more recent cases were given dicoumarin without effect.

6. Since January 1944 nine cases of subacute bacterial endocarditis have been treated with large doses of penicillin. The results to date are as follows:

a. Two of the nine cases have died, one of cerebral embolism during the course of treatment and the second of rheumatic fever eight months after the completion of therapy, apparently bacteriologically "cured."

b. One case seems clinically free from infection but has severe congestive failure.

c. One case who had to return for a second course of therapy has now been having low grade fever for two days so that his present status is uncertain. He may have active rheumatic fever.

d. One case was well for one month after the completion of therapy but

returned on December 12 because of low grade evening rise of temperature. He showed a recurrence of subacute bacterial endocarditis, but at present (December 29) is again controlled by penicillin and sulfadiazine in combination.

e. Four cases are apparently well. Three are clinical and bacteriological "cures" seven weeks, five months, and eight months after the completion of therapy, and the fourth is well two months after a second three weeks' course of penicillin given for recurrence of the infection.

f. Thus six of these nine cases (67%) have shown a definite control (perhaps a cure) of their subacute bacterial endocarditis by "massive" doses of penicillin; two of these six cases, however, developed other serious complications, namely rheumatic fever and congestive heart failure respectively.

g. A follow-up note of this series will be presented at the end of another year, at which time a more accurate appraisal can be given.

7. Important complications of subacute bacterial endocarditis that tend to be too little emphasized are cerebral embolism, acute rheumatic infection, and congestive failure, alone or in combination. At the present time these three conditions, as noted above, are on occasion serious drawbacks to complete recovery, even in the very cases that seem to be reacting so well to the massive penicillin therapy.

The authors acknowledge with thanks the kindness of Massachusetts General Hospital staff members in permitting the inclusion of the records of several of their private patients in the series of cases herewith reported, and of Dr. Chester Keefer in supplying the penicillin in more ample dosage for the cases treated with that drug during the early months of 1944.

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OBSERVATIONS ON THE TREATMENT OF SUBACUTE BACTERIAL (STREPTOCOCCAL) ENDOCARDITIS SINCE 1939 *

By SAUL R. KELSON, CAPTAIN, M. C., A. U. S., *Augusta, Georgia*

ANALYSIS of 250 well-authenticated cases of subacute bacterial (streptococcal) endocarditis studied during the years from 1927 to 1939 disclosed the ineffectiveness of all methods of therapy prior to the introduction of the sulfonamide drugs.[1] Sulfanilamide and particularly sulfapyridine appeared favorably to influence the course of the infection; in some instances, reduced fever and negative blood cultures temporarily followed the use of these drugs. Subsequent experience in the treatment of this disease has made clearer the effects of sulfanilamide and its derivatives, which are shown in the following summary. Some of the cases treated with sulfanilamide and sulfapyridine were collected from other clinics by Dr. Paul D. White and the author; the others were treated personally. Only instances in which the drugs were given prolonged and intensive trials have been included.

Sulfanilamide. Used in *52* patients, the drug occasionally reduced the fever and rendered blood cultures negative, but no lasting benefit resulted in any instance.

Sulfapyridine. In *197* patients, this drug lowered the temperature in a majority, with blood cultures frequently becoming negative. Except in four instances, however, these effects were transitory, lasting from a few days to two months. The four cases apparently cured were caused by the gonococcus together with a non-hemolytic anerobic streptococcus in one instance,[2] and by the *Streptococcus viridans* in the others.[3, 4]

Sulfathiazole. In *23* cases, this drug gave temporary improvement in four.

Sulfadiazine. In *12* cases, this drug gave temporary benefit in two.

On the basis of the finding by White and Parker [5, 6] that the sulfonamide drugs have greater antibacterial activity at higher temperatures, Solomon proposed the use of sulfapyridine or sulfanilamide in combination with intravenous typho-paratyphoid vaccine.[7] We have followed this method, using sulfapyridine—in some instances supplemented with related drugs—together with injections of the vaccine, intensively in *12* patients, with transitory benefit in three.

As a result of its effectiveness in bacteriostatic tests in tissue-culture,[8] Osgood advocated the use of neoarsphenamine, alone or in conjunction with sulfathiazole.[9] We have administered this treatment to eight patients without benefit.

In addition to these measures, we have tried a variety of others, all

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without success: sulfamethylthiazole, acetyl sulfanilamide (Sulamyd), sulfhydrothiazole, two or more sulfonamide drugs in combination, hyperthermia combined with the sulfonamides, precordial diathermy with the sulfonamides, typhoid vaccine with heparin and the sulfonamides, autotransfusion of blood irradiated with ultraviolet light, induced anaphylactoid shock, and in two cases intravenous injections of tyrothricin (gramicidin plus tyrocidine).

Apparent Recoveries Since 1939

To supplement this experience of our own and further to evaluate the status of treatment, we have analyzed and tabulated the apparent recoveries from subacute bacterial (streptococcal) endocarditis as reported from 1939 to the present time (August 1944) (table 1).* A critical search of the literature disclosed a number of other cases which could not be included as authentic instances of recovery from this disease. Some had had no positive blood cultures. Others lacked the clinical picture of bacterial endocarditis—presenting at times the findings of rheumatic fever or even of a blood dyscrasia, and the diagnoses were based primarily on one or two positive cultures, which, clearly, were incidental bacteremias. Still other cases reported as cured were lost from observation after brief periods.† Progress in the treatment of this disease requires accurate diagnosis and careful follow-up of patients. No attempt has been made to evaluate the various methods of treatment on the basis of the percentage of apparent recoveries in pooled statistics; successes are apt to be reported and failures not, though the failures of new or unusual methods are more likely to appear in print than those of simpler, virtually routine measures like the use of the sulfonamides alone. More important, among such groups of cases are a large number allegedly treated by a previously described technic, but in fact given widely different therapy. This has been strikingly true of many cases reported as using the sulfapyridine-heparin method, but in effect employing heparin alone, often because that drug was administered well after sulfapyridine had been begun and had spent its action. Such cases, and those treated with insufficient care or persistency, by no means constitute a valid test of any advocated method.‡

* Unreported cases—some mentioned in the literature as having been treated by other workers, but not described—undoubtedly have been treated successfully, but are difficult to collect and analyze and impossible for the reader to study and verify, and so are omitted.

† Some patients were again showing evidence of infection at the time of premature publication of their "recovery," or did so shortly afterward.

‡ Illustrative of such cases from which statistics are made and methods of therapy judged is a series of four recently reported [10] as examples (and failures) of combined heparin-sulfonamide treatment. In case 1, nausea followed the use of sulfapyridine, which was discontinued, apparently on the same day; heparin, begun two days later, was given for seven days *without* accompanying chemotherapy. In case 2, sulfanilamide and sulfathiazole failed to influence the infection, but nevertheless heparin was continued with these drugs for six weeks. In case 3, sulfapyridine was omitted because of nausea and vomiting, and heparin given for nine days along with sulfathiazole, which was ineffective. In case 4, sulfapyridine was given for seven days by rectum, with low (1.7 mg. per cent) blood concentration, and then, after a lapse of five days, resumed by vein (with blood cultures remaining positive) for four days; heparin was given only during these four days, and a fifth. For five days during heparinization, patient 2 also received arsenical therapy, as did patient 3 in the month following discontinuance of heparin.

TABLE I

Apparent Recoveries from Subacute Bacterial (Streptococcal) Endocarditis Reported since 1939

Author	Number of Cases	Underlying Heart Disease	Specific Treatment	Reference
WELCH, F. E., and SOUTHWOOD, A. R.	1	Rheumatic, mitral	None	Med. Jr. Australia, 1939, i, 392.
LONG, P. H., and BLISS, E. A.(i)	4 1	Congenital Rheumatic, mitral	Sulfanilamide	Clinical use of sulfanilamide and sulfapyridine and allied compounds, 1939, Macmillan, New York, p. 179.
MAJOR, R. H., and LEGER, L. H.	1	Rheumatic, mitral	Neoprontosil and sulfapyridine	Jr. Kansas Med. Soc., 1939, xl, 324.
SPINK, W. W., and CRAGO, L. H.	1	Patent ductus arteriosus	Sulfanilamide	Arch. Int. Med., 1939, lxiv, 228.
BARTON, R. L., and STINGER, D.	1	Congenital?	Sulfanilamide	Jr. Iowa State Med. Soc., 1939, xxix, 402.
ORGAIN, E. S., and POSTON, M. A.(ii)	1	Apparently none. Implantation on pulmonic valve.	Sulfapyridine	New England Jr. Med., 1939, ccxxi, 167.
KELSON, S. R., and WHITE, P. D.	1 1	Rheumatic, mitral and aortic Rheumatic, mitral	Sulfapyridine and heparin	Jr. Am. Med. Assoc., 1939, cxiii, 1700.
MAJOR, R. H.	1	Rheumatic, mitral	Sulfapyridine	Am. Jr. Med. Sci., 1940, cxcix, 759
HEYMAN, J.	1	Patent ductus arteriosus	Sulfanilamide	Jr. Am. Med. Assoc., 1940, cxiv, 2373.
TOUROFF, A. S. W., and VESSELL, H.	1	Patent ductus arteriosus	Surgical closure	Jr. Am. Med. Assoc., 1940, cxv, 1270.

(i) These five cases were among the first group of "more than 60" observed by these authors. Two more apparent recoveries occurred when the group had enlarged to 117. The additional cases have not been reported.

(ii) This was a typical case of gonococcal endocarditis, and was reported as such. It is included here because a non-hemolytic anaerobic streptococcus was also constantly present in the blood cultures.

TABLE I—*Continued*

Author	Number of Cases	Underlying Heart Disease	Specific Treatment	Reference
CHRISTIE, A.	1	Rheumatic, mitral	Sulfanilamide	Jr. Am. Med. Assoc., 1940, cxv, 1357.
DOANE, J. C.	1	Rheumatic, mitral	Sulfapyridine and heparin	New Internat. Clin., 1940, iv, Ser. 3.
COLVIN, L. T.	1	Rheumatic, mitral	Sulfanilamide and sodium cacodylate	Jr. Mich. State Med. Soc., 1940, xxxix, 946.
ORGAIN, E. S., and POSTON, M. A.	1	Rheumatic, aortic, ?mitral	Sodium sulfapyridine	North Carolina Med. Jr., 1941, ii, 24.
SOLOMON, H. A.	1	Rheumatic, mitral	Sulfanilamide and intravenous typhoparatyphoid vaccine	New York State Jr. Med., 1941, xli, 45.
	3	Rheumatic, mitral and aortic	Sulfapyridine and intravenous typhoparatyphoid vaccine	
LICHTMAN, S. S., and BIERMAN, W.	1	Rheumatic, mitral [iii]	Sulfapyridine and heparin	Jr. Am. Med. Assoc., 1941, cxvi, 286.
	1	—	Sulfanilamide and sulfapyridine and heparin [iv]	
BIERMAN, W., and BAEHR, G.	1	Rheumatic, mitral	Radiotherapy, sulfanilamide and hyperthermia.	Jr. Am. Med. Assoc., 1941, cxvi, 292.
	1	—	Sulfanilamide and hyperthermia	
MUDD, J. L.	1	Patent ductus arteriosus	Surgical closure	Weekly Bull. St. Louis Med. Soc., 1941, xxxv, 304.
HEYER, H. E., and HICK, F. K.	1	Coarctation of the aorta	Sulfanilamide	Ann. Int. Med., 1941, xv, 291.
WEBER, F. PARKES	1	Rheumatic, mitral	None	Lancet, 1941, i, 630.
DRUCKMAN, J. S.	1	Rheumatic, mitral	Neoarsphenamine, sulfapyridine, sulfamethylthiazole and heparin	Jr. Am. Med. Assoc., 1941, cxvii, 101.

[iii] This patient, treated by the author (S. R. K.), is listed also in table 2, as case 2.
[iv] The authors did not consider that heparin used in the therapy of this patient had had an appreciable effect on blood coagulation.

TABLE I—*Continued*

Author	Number of Cases	Underlying Heart Disease	Specific Treatment	Reference
JERSILD, M.	1	Rheumatic, mitral	Sulfamethylthiazole	Ugesk. f. Laeger, 1941, ciii, 1261.
BOURNE, G., KEELE, K. D., and TUBBS, O. S.	1	Patent ductus arteriosus	Surgical closure and sulfapyridine	Lancet, 1941, ccxli, 444.
LEACH, C. E., ET AL.	1	Patent ductus arteriosus	Sulfapyridine, heparin and sulfathiazole [v]	Jr. Am. Med. Assoc., 1941, cxvii, 1345.
	1	Rheumatic, aortic	Sulfathiazole	
GROSS, R. E.	2	Patent ductus arteriosus	Sulfonamides and surgical closure	Modern concepts of cardiovascular disease, 1941, No. 12, 10 (Dec.).
FIELD, H., JR., HOOBLER, S. W., and AVERY, N. L., JR.	1	Tetralogy of Fallot	Sulfapyridine	Am. Jr. Med. Sci., 1941, ccii, 798.
BICKEL, G., and MOZER, J. J.	1	Rheumatic, mitral	Sulfathiazole	Rev. Med. de la Suisse, 1941, lxi, 474.
TOUROFF, A. S. W., VESSELL, H., and CHASSNOFF, J.	1	Patent ductus arteriosus	Surgical closure	Jr. Am. Med. Assoc., 1942, cxviii, 890.
OSGOOD, E. E.	3	—	Neoarsphenamine, or neoarsphenamine and sulfathiazole	Arch. Int. Med., 1942, lxix, 746.
SMITH, C., SAULS, H. C., and STONE, C. F.	1	Patent ductus arteriosus	Sulfanilamide	Jr. Am. Med. Assoc., 1942, cxix, 478.
TOUROFF, A. S. W., and TUCHMAN, L. R.	1	Patent ductus arteriosus	Surgical closure	Am. Heart Jr., 1942, xxiii, 847.
CHRISTIE, A., and PARKER, A.	1	Congenital	Sulfanilamide and sulfathiazole	Clinics, 1942, i, 677
HUMPHREYS, G. H.	1	Patent ductus arteriosus	Surgical closure	Surgery, 1942, xii, 841.
	1	Patent ductus arteriosus	Sulfonamide and surgical closure	

[v] Six months after disappearance of all evidence of infection and one month after discontinuance of therapy in this patient, the ductus arteriosus was closed surgically by Dr. Robert E. Gross. Four months later, the patient was killed in an automobile accident, and autopsy revealed complete healing of the bacterial lesion.

TABLE I—*Continued*

Author	Number of Cases	Underlying Heart Disease	Specific Treatment	Reference
DAYTON, A. B., and LINDSKOG, G. E.	1	Patent ductus arteriosus	Sulfadiazine and surgical closure	Yale Jr. Biol. and Med., 1942, xv, 259.
WINN, W. A., HUGHES, C. L., and SANDERS, J. M.	1	Patent ductus arteriosus	Sulfapyridine and heparin	Ann. Int. Med., 1943, xviii, 242.
TOUROFF, A. S. W.	3	Patent ductus arteriosus	Surgical closure	Am. Heart Jr., 1943, xxv, 187.
HARRINGTON, S. W.	1	Patent ductus arteriosus	Surgical closure	Proc. Staff Meet. Mayo Clin., 1943, xviii, 217.
GROSS, R. E.	3	Patent ductus arteriosus	Surgical closure	New York State Jr. Med., 1943, xliii, 1856.
NIXON, J. W., BONDURANT, W. W., JR., and ROAN, O.	1	Patent ductus arteriosus	Surgical closure	Ann. Int. Med., 1943, xix, 1003.
LOEWE, L., ROSENBLATT, P., GREENE, H. J., and RUSSELL, M.	2 2 2	Rheumatic, mitral Rheumatic, aortic Rheumatic, mitral and aortic [vii]	Penicillin and heparin [vi]	Jr. Am. Med. Assoc., 1944, cxxiv, 144.
DAWSON, M. H., and HOBBY, G. L.	2	Rheumatic	Penicillin	Jr. Am. Med. Assoc., 1944, cxxiv, 611.
BUNN, W. H.	1 1	Rheumatic, aortic Patent ductus arteriosus	Sulfathiazole Sulfathiazole and sulfadiazine	Jr. Am. Med. Assoc., 1944, cxxv, 1023.

[vi] All these patients had been given sulfonamide therapy previously; one also received sulfonamides between courses of penicillin and heparin, and another, for a time during the administration of these drugs.

[vii] One of these cases, though caused by a hemolytic streptococcus, showed a subacute rather than an acute course.

Cases of streptococcal endarteritis of the patent ductus arteriosus treated by operative closure, it is seen, hold an impressive place on the list of apparent recoveries, quite disproportionate to their relative frequency (five of the 250 cases of subacute bacterial (streptococcal) endocarditis and endarteritis collected by the author and White [1]). Surgical technic has progressed to make this procedure relatively safe and sure, giving a high percentage of apparent cures. The stimulating questions of the mechanisms of recovery in these cases and of the possible prophylactic value against bacterial endarteritis of ligating the non-infected ductus are discussed elsewhere.[1]

Sulfapyridine in Subacute Bacterial (Streptococcal) Endocarditis

Of the methods of treatment noted in our own experience, sulfapyridine proved the most active in lowering the temperature * and in producing negative blood cultures.† Except in the four instances cited among the 197 treated cases, however, its effects were no more than transient. The failures of the drug to cure appear related to the following factors:

1. Death occurs at times from embolism or congestive heart failure in spite of even a strong action of the drug in controlling the infection.
2. Rarely, toxic effects of the drug itself are fatal.‡
3. The action of drugs of this group is bacteriostatic, rather than bactericidal, and they require phagocytes for the final killing of the organisms. The paucity or absence of polymorphonuclear leukocytes in proximity to the

* Some have called this drop in temperature only an "antipyretic effect," implying that sulfapyridine reduces fever in this disease solely by an action on the temperature-regulating center and not by any direct bacteriostasis of streptococci. This response, however, parallels other evidences of effectiveness of the drug: it has occurred, in most cases strikingly from the start, and has been sustained in our patients who, with the additional use of heparin, have gone on to recovery; in others, it has been absent, slight, or transient, except in those who have responded as well as the group just noted, remaining afebrile and culture-negative for as long as two months, but have received no heparin and "escaped" from the sulfapyridine effect. Fall in temperature is the rule with the disappearance of bacteremia following medication; if fever recurs, one can foretell that blood cultures again will be found positive (unless the pyrexia has another cause: embolism, drug sensitivity rarely, intercurrent infection like nasopharyngitis not responding to the drug, etc.) Swain [11] and Orgain and Poston,[12] moreover, have shown a definite correlation between the in vitro bacteriostatic power of the sulfonamides on strains of *Streptococcus viridans* and their effectiveness in treatment (including reduction of fever). Sulfapyridine acts strongly on many of these strains, and in bacterial endocarditis, as in pneumonia and meningitis, fall in temperature is a prime index of the response to specific therapy.

† This is true sterilization of the blood stream, and not merely inhibition of the growth of organisms in the culture media by drug present in the drawn blood, for at no time in our experience has the addition of paraaminobenzoic acid secured positive cultures when cultures were negative without it.

‡ Sometimes grave side-actions of the drug make its continuance impossible. More often, disagreeable and perhaps injurious but less severe toxic effects are the reason for omitting the drug; as stressed below, failure to persist in administering sulfapyridine in the combined therapy with heparin in the face of any but the most serious side-effects has sacrificed the chance of possible cure.

bacteria within the vegetations makes this a decisive factor in the treatment of this disease.†

4. The drug may penetrate in insufficient concentration to the organisms within the bacterial vegetations. Duncan and Faulkner [14] found that sulfapyridine fails to enter blood clot in vitro, but Uhley and Katz,[15] on the contrary, demonstrated that it does permeate through a fibrin barrier.‡ Results of such test-tube experiments with these structures, similar to but not identical with bacterial vegetations, may or may not have validity within the living body. Vegetations, it must be remembered also, constantly are being worn down and laid open by embolization. The problem of contact of drug with organisms can not be considered as settled; the phenomenon of acquired resistance (see 6, below) and the occurrence of recoveries with the use of the drug alone or in combined therapy show that contact does occur; but it is likely that it is variable, and may be much restricted. As pointed out,[40] the presence in the vegetation of tissue debris, shown by Lockwood and his co-workers [16a] to inactivate sulfonamides, also may decrease the "effective concentration" of the drug.

5. Some strains of non-hemolytic streptococci fail to respond to the action of the drug from the start of treatment. Swain,[11] Poston and Orgain,[17] and others have shown that the many different strains of these organisms vary widely in susceptibility to the bacteriostatic action of sulfapyridine and related drugs. One or more sulfonamides inhibited the growth in vitro of 17 among 25 strains of *Streptococcus viridans* which Poston and Orgain tested, but against eight no drug was active. These drugs are particularly ineffective against the enterococci.[18]

6. Other strains of non-hemolytic streptococci, susceptible to sulfapyridine from the beginning of treatment, later become resistant to its action. In all but four of the cases which had shown an initial response to sulfapyridine, fever and bacteremia, as noted, recurred in from a few days to two months. This clinical "escape" from sulfapyridine effect, which Whitby [19] pointed out in the disease, was stressed early by the present author.[13, 20]

In 1938, Cokkinis and McElligott [21] observed that when patients with gonorrhea were treated with inadequate dosages of sulfanilamide, or particularly, when the drug was discontinued too early, the relapses which followed were highly refractory to further treatment with sulfanilamide. They

† The problems involved in treatment are discussed in another publication.[13]

‡ Friedman [16] found limited penetration of sulfapyridine and sulfanilamide through fibrin-platelet membranes in vitro. Fibrin-platelet masses infected with *Streptococcus viridans* and placed in permeable capsules implanted within the abdominal cavities of rabbits were not sterilized by prolonged intravenous and intraperitoneal administration of sodium sulfapyridine or sulfanilamide. These experiments, however, did not actually determine the in vitro penetrability of fibrin-platelet masses by these drugs, for the drugs likewise failed to sterilize, and indeed had but little effect on the growth of organisms placed directly—in the absence of fibrin-platelet masses—into such filter-capsules within the peritoneal cavity. Only when the drugs had been added to the capsules *before* their implantation—thus eliminating a "lag phase" in building up a concentration of drug within the capsules—were some of the inocula sterilized.

named this phenomenon "acquired resistance." Its mechanism was clarified by the demonstration [22, 23, 24, 25] that organisms could be made insusceptible to the sulfonamide drugs. Pneumococci sensitive to sulfapyridine, for example, were rendered markedly resistant by growing them in the presence of increasing concentrations of the drug in vitro, or passing them through series of mice given less than curative amounts of sulfapyridine. The resulting "fast" organisms were unchanged in morphology, virulence, growth away from the drug, type specificity, and susceptibility to serum.[23, 26] Resistance can be lost when only partially developed, Schmidt and his associates found, but when established it persists almost indefinitely, having remained for 200 passages through untreated mice.[26] Organisms rendered resistant in vitro remain so in vivo, and conversely.[26] Pneumococci made resistant to one sulfonamide are resistant also in vitro and in vivo to other sulfonamides.[25, 26, 27, 28, 29] * Different strains of an organism varied in their ability to develop fastness,[29] and an individual strain acquired resistance to the various drugs at different rates, doing so most rapidly to the least effective and least rapidly to the drug with the greatest effect.[29, 30]

Schmidt and Sesler [31] concluded that sulfonamide-resistant forms result from an action of the drug on the sensitive organisms, and not from the normal multiplication of such organisms. MacLeod [32] showed early that alterations in the intermediary metabolism of the bacteria accompany the development of fastness, with a marked decrease in the production of hydrogen peroxide and in the oxidation of glycerol, pyruvate, and lactate. He later [33] demonstrated that these resistant organisms synthesize increased amounts of sulfonamide inhibitor. Mirick [34] identified this as paraaminobenzoic acid, of which, he found, resistant pneumococci produce 10 times as much as do the parent strains. Resistant staphylococci, Landy and his group showed,[35] elaborate this inhibitor in 70 times the usual amounts, and continue to produce a great excess.

That sulfonamide-sensitive organisms may become sulfonamide-resistant in the course of clinical treatment has been demonstrated repeatedly. In a case of pneumococcal meningitis treated with sulfapyridine,[36] for example, and in one of type VII pneumococcal endocarditis treated with sulfapyrazine,[37] both of which had shown an early response to the drugs and a later absence of effect, in vitro tests showed the initial organisms susceptible to the respective drugs, but those isolated after therapy to be resistant. Lowell,

* Clinically, we have seen responses to sulfapyridine after the development of resistance to other sulfonamides, but the latter drugs have been ineffective following sulfapyridine "escape." This accords with the finding by Kirby and Rantz [28] that the degree of resistance correlates directly with the bacteriostatic power of the drug. Apparently sulfapyridine, the more active drug, could overcome the lesser resistance imparted by the less active drugs, but their bacteriostatic power was insufficient to overcome the greater fastness which it had produced. In our experience, increasing the blood concentration of sulfapyridine after infection had become resistant to a given level resulted at times in reducing the temperature—especially with very high concentrations—but never produced sterilization of the blood stream. This is at variance with the finding by the above authors that organisms resistant to lower concentrations of a drug may be susceptible to higher levels, but accords with earlier observations.

Strauss, and Finland [25] found type II pneumococci isolated from each of two patients at the beginning of pneumonia therapy to be highly sensitive to sulfapyridine, and to sulfathiazole and sulfamethylthiazole; after relapse had occurred in one patient during sulfapyridine therapy and in the other shortly after discontinuing this drug, the organisms then isolated were found highly resistant in vitro to all three drugs. In a case of type VII pneumococcal pneumonia,[38] the bacteria, originally sensitive, became resistant to sulfadiazine during treatment; transmitted by contact to a second patient, they produced pneumonia which also was resistant to sulfadiazine, and both patients were shown later to carry in their throats these virulent sulfadiazine-fast pneumococci. In one report of striking interest,[39] endocarditis developed in a horse during immunization with type A hemolytic streptococci for the production of antistreptococcal serum. Sulfanilamide failed to overcome the bacteremia, and the animal died on the eleventh day of treatment. Streptococci from the blood showed a progressive increase of resistance to sulfanilamide, and those isolated the day of death were much more resistant than the stock culture. Organisms from the valvular vegetations were less resistant than these last ones from the blood, but more so than the original strain, a finding which was explained by the lower concentrations of drug to which these organisms in the vegetations were exposed, as compared to those in the blood stream.

Hamburger and his co-workers [40] conclude that resistance is most likely to develop when the nature of the lesion prevents complete eradication of the bacteria, yet permits limited exposure to the drug. Endocarditis provides ideal conditions for this, they point out; organisms can become moderately resistant from contact with the lower concentration of drug within the vegetations, enabling them to survive in the higher levels in the blood stream, contact with which, in turn, produces even greater fastness. Resistant pneumococci arise infrequently, they state, during brief treatment, such as is usual in pneumonia, but in prolonged treatment, as in endocarditis, they appear to develop regularly. In treating subacute bacterial (streptococcal) endocarditis, we have found "acquired fastness" to take place almost invariably, often after even brief medication. In the use of sulfapyridine alone, and—as will be noted presently—in combined therapy, it is a phenomenon of the first importance.

Heparin and Chemotherapy in Subacute Bacterial (Streptococcal) Endocarditis

In November 1939 the author and White introduced a new method of treatment of subacute bacterial endocarditis, using heparin and chemotherapy in combination.[13] We employed heparin, a powerful anticoagulant which had been shown to arrest the deposition of platelets and fibrin, in an attempt to prevent further thrombotic deposits on (and in) the vegetations. This could restrict the nidus and culture medium for bacterial growth, and

prevent embolism from the detaching of fresh thrombus; particularly, checking the enlargement of the vegetations could enable the fibroblasts present at their base to heal the areas thus limited. There was no evidence that heparin could dissolve the vegetations, or that it could increase their permeability to sulfapyridine (the chemotherapeutic agent used), except as reduced platelet and fibrin deposition itself might have this effect.

We emphasized the *combined* nature of this new attack, and the necessity of an accompanying strong action of the chemotherapeutic drug.[13, 20] Further experience has stressed this still more forcibly. Without such an accompanying action, heparin has not been curative, even when administered for as long as three weeks (or, as in one reported case,[10] for six); it has been useful only in those cases in which sulfapyridine (or a related drug) was able to reduce the temperature to normal or near it and to sterilize the blood stream. Some have questioned the value of heparin, when the chemotherapy of itself can produce this result, and heparin can not. Yet—and this is the crucial point—sulfapyridine frequently (and related drugs less often) abolishes fever and bacteremia, even for two months, but when it is discontinued, or, usually, as it is being given, these manifestations of active infection almost invariably recur, and recovery has rarely taken place. If, however, blood coagulability has been decreased during such a period (two weeks, or at times less) of strong bacteriostatic response to a sulfonamide, recovery—with but one exception in our experience—has resulted.

Heparin, we have found, has regularly produced the desired decrease of blood coagulability.* The great problem has been in securing the accompanying antibacterial effect. Some strains of non-hemolytic streptococci, as noted, are insusceptible to sulfonamide action from the start; but—more significant because it is preventable—previous medication during the present illness had rendered the streptococci of many patients drug-resistant. If sulfapyridine had already been given and "escape" had occurred (and frequently if the drug had been discontinued while still active), its further use as a rule produced but little effect; at times the temperature could be lowered, especially by very large doses, but blood cultures rarely could be rendered negative. If the organisms failed to respond to sulfapyridine, moreover, we have never obtained later adequate responses to other sulfonamides.† Most striking and regrettable were the cases which had excellent

* I have not used dicoumarol in the combined therapy, or known of its use when the accompanying bacteriostasis has been strong. Though having the convenience of oral administration, dicoumarol lacks the responsiveness to control of heparin: a long latent period, 24 hours or more, elapses before it becomes effective, and its action passes off gradually after it has been discontinued. Several investigators have stressed its toxic actions, particularly in causing bleeding.

Intracranial hemorrhages have been described with the use of heparin in this disease, and we have seen them take place during heparinization in three of 40 patients. Cerebral deaths occur commonly, however, as a complication of the endocarditis itself, as a result of embolism; the frequency of such deaths has not been increased in our patients under heparin therapy. This problem will be discussed in a later article.[41]

† Satisfactory responses to sulfapyridine have been seen, however, following "escape" from the action of other sulfonamide drugs.

responses in the past, but which were found resistant to further medication when brought to us for combined therapy.* If this treatment was contemplated, it was most important to withhold sulfapyridine until both drugs could be given; even in small amounts and for brief periods, it apparently could produce fastness, and all chance of success was lost. In patients previously untreated with sulfapyridine, approximately one-half gave the desired bacteriostatic response. The first rule of success with the combined therapy, then, has been the avoidance of the previous use of sulfapyridine. The second rule has been the persistent continuance of treatment, even in the face of all but the most dangerous toxic effects of the sulfapyridine and of grave turns of the disease itself. Repeatedly we have observed all chance of cure sacrificed by interrupting or discontinuing sulfapyridine at a time of good response (or before its effect could be shown) because the patient developed nausea and vomiting, a skin rash, or a falling erythrocyte count. In some of our patients, now living and well more than two years later, we pressed on with treatment even though intractable vomiting demanded medication and glucose solutions by vein and morphine in narcotic doses, or —in one striking instance (table 2, case 7)—despite continuous severe hematuria from renal concretions of sulfapyridine, necessitating blood transfusion.

Of our originally reported group of patients, two are listed among the apparent recoveries noted in table 1. In the first of these, all evidence of *Streptococcus viridans* endocarditis disappeared following sulfapyridine-heparin therapy, but a concurrent rheumatic infection persisted and the patient died in congestive heart failure six months later. Autopsy disclosed acute and chronic rheumatic endocarditis and myocarditis, and completely healed calcified and fibrosed vegetations of bacterial endocarditis, free of streptococci, on the mitral valve. The second patient has remained well and active except for an attack of rheumatic fever in 1944. She has shown no evidence of bacterial endocarditis for over five years now, since completion of therapy on May 26, 1939.

Table 2 presents 10 additional apparent recoveries among the 34 patients with subacute bacterial (streptococcal) endocarditis, treated subsequently with heparin and chemotherapy by the author. All were clinically definite cases, having had two blood cultures positive for *Streptococcus viridans* in two instances and three or more in the others. In patient 1, in whom all manifestations of the disease disappeared following therapy, with restoration of vigorous well-being and a gain of 46 pounds in weight, bacterial endocarditis recurred directly after the removal of two abscessed teeth three months later, and treatment then was unavailing. Postmortem examination showed healed and fresh vegetations which confirmed the clinical belief that

* As the "effective concentration" of drug in the vegetations falls after stopping medication, organisms there can withstand these lowered levels, contact with which apparently produces a resistance enabling them to grow, on resuming the drug, in previously bacteriostatic concentrations. In one patient, for example, afebrile and culture-negative for two months while receiving sulfapyridine, fever and bacteremia recurred one day after omitting the drug, and it had no effect when resumed three days later.

TABLE II

Further Apparent Recoveries among 34 Patients with Subacute Bacterial (Streptococcal) Endocarditis Treated by the Author with Combined Chemotherapy and Heparin

No.	Patient	Age Sex	Duration of Infection	Underlying Heart Disease	Specific Treatment	Treatment Completed	Outcome
1	W. E. D.	33 M	4 mos.	Rheumatic, aortic	Sulfapyridine and heparin *	March, 1940	Well, active and without evidence of disease after completion of therapy, with 46 lb. gain in weight. Reinfection directly followed extraction of two abscessed teeth three months later. Autopsy showed healed and fresh lesions of subacute bacterial endocarditis.
2	J. Z.	33 M	5 mos.	Rheumatic, mitral	Sulfapyridine and heparin	April, 1940	Well, active and without evidence of disease since completion of therapy.
3	L. B.	30 F	4 mos.	Rheumatic, mitral	Sulfapyridine and heparin	June, 1940	Well, active and without evidence of disease since completion of therapy.
4	L. L.	45 M	1½ mos.	Rheumatic, mitral	Sulfapyridine, sulfadiazine and heparin	March, 1941	Well, active and without evidence of disease after completion of therapy. Sudden death, when no evidence of infection was present, on July 25, 1943.
5	G. B.	30 F	1 mo.	Rheumatic, mitral	Sulfapyridine and heparin	Sept., 1941	Well, active and without evidence of disease since completion of therapy.
6	P. V.	31 M	5 mos.	Rheumatic, mitral	Sulfadiazine and heparin	Dec. 1941	Well, active and without evidence of disease since completion of therapy.
7	G. P.	22 F	2 mos.	Rheumatic, mitral	Sulfapyridine and heparin	March, 1942	Well, active and without evidence of disease since completion of therapy.
8	B. P.	19 M	1 mo.	Rheumatic, mitral	Sulfapyridine and heparin	April, 1942	Well, active and without evidence of disease since completion of therapy.
9	G. A.	29 F	2 mos.	Rheumatic, mitral and aortic	Sulfapyridine and heparin	April, 1942	Well, active and without evidence of disease since completion of therapy.
10	E. L.	40 M	5½ mos.	Rheumatic, mitral and aortic	Penicillin, sulfadiazine and heparin	Nov. 1943	Well, active and without evidence of disease since completion of therapy.

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* In this and most of the following cases sulfapyridine was given in part by vein, as sodium sulfapyridine.

the patient had had a second attack of the disease, precipitated by dental extraction, after he had recovered from his original infection. Patient 4 remained well and active following completion of therapy and showed no further evidence of the disease. Twenty-eight months later, while up and about and feeling perfectly well, he suddenly collapsed and was dead within a few minutes. There was no autopsy. Except for this patient, cases 2 through 9, it is seen, have remained well now from over two years to more than four years. Case 10, treated more recently (November 1943), is discussed later in this paper (page 91). These cases will be presented in full in a further report [41] dealing with the results, principles, and technic of therapy.

Conservation of the bacteriostatic effect of sulfapyridine for its use at the time of heparinization, and greater persistency in the administration of the drugs can increase the proportion of recoveries from this combined method of therapy. Improvements in technic, too, may do so. Further progress lies particularly in the development of sulfonamide or other drugs which are more active than sulfapyridine against the strains of non-hemolytic streptococci and effective against more of these strains, and which are less toxic. To date, no newer sulfonamide drugs have been found to possess these superiorities.* Another chemotherapeutic agent, however, of different origin and mode of action—penicillin—now holds much promise in the treatment of this disease.

Penicillin in Subacute Bacterial (Streptococcal) Endocarditis

The keenest of interest in the treatment of subacute bacterial endocarditis now centers about penicillin. In his original description of the substance, Fleming [44] listed the *Streptococcus viridans* among the organisms sensitive to its action, and later workers [45, 46, 47, 48] have confirmed this in vitro antibacterial effect. Bornstein [45] found that penicillin inhibited each of 13 cultures of *Streptococcus viridans,* including three isolated from endocarditis patients, though against 27 strains of enterococci he found it ineffective, as had Fleming. Heilman and Herrell [47] showed that three strains of *Streptococcus salivarius* were totally inhibited in tissue culture by penicillin in concentrations of 40 micrograms per cubic centimeter (the order of sulfonamide inhibition). Dawson and his co-workers [50] compared the in vitro sensitivity to penicillin of strains of non-hemolytic streptococci from bacterial endocarditis cases with that of a standard strain of hemolytic strepto-

* Sulfadiazine, though very much less toxic, in our experience has been less effective than sulfapyridine, though probably is second to it. We have not used sulfamerazine, sulfamethazine, or sulfapyrazine in treating endocarditis caused by non-hemolytic streptococci, and data concerning their use are meagre. Hall and Spink [42] found that sodium sulfamerazine failed to sterilize the blood in one *Streptococcus viridans* endocarditis case. Sulfamerazine was unsuccessful in all four cases infected with the same organisms, treated by Flippin and his co-workers.[43] In a case noted by Anderson, Oliver, and Keefer,[43a] after 10 days of sulfamerazine with blood levels about 15 mg. per cent, blood cultures became negative and remained so for 20 days, then were positive despite continuing treatment. Three more advanced cases, with lower drug levels, were not benefited.

coccus. Of 41 such strains (17 of them *viridans*), they found one twice as sensitive, eight equally sensitive, 23 one-fourth to one-half, four one-eighth, two one-sixteenth, and one one-sixty-fourth as sensitive as the standard, and only two—one of them being one of two strains "resembling enterococci"—resistant. The sensitivity of a strain, they found, was not correlated with its cultural or serological properties.

Several reports [49, 51, 52, 53] of the use of penicillin in subacute bacterial (streptococcal) endocarditis indicate a reduction of fever and sterilization of the blood, but in nearly all cases fever and bacteremia have recurred on discontinuing the drug. A patient of Herrell's,[51] for example, infected with a *Streptococcus viridans* inhibited in vitro in dilutions of 1 : 500,000 of penicillin, became afebrile and culture-negative six hours after beginning a constant intravenous drip of the drug; cultures continued negative during the six days of administering 128,000 units, but four to six hours after completing therapy bacteria reappeared in the blood. Of 10 *Streptococcus viridans* cases which Dawson treated with penicillin, five, given very small amounts, in preliminary trials, showed no significant results, and a later patient with doses believed insufficient (a total of 975,000 units for three interrupted periods of five days each), was not benefited. Treatment failed in another, despite almost eight million units over 33 days; the blood cultures, temporarily negative, were positive at the time of death from cerebral embolism. Two patients, given 830,000 units over 10 days and 1,420,000 units over 23 days, however, were reported as alive and well for 13 and nine months, respectively, after discontinuing therapy. In one case of exceptional interest, the infection responded to penicillin on every one of numerous occasions, but recurred within two or three weeks after each discontinuance of the drug, and persisted after nearly seven million units had been administered. In a report for the Committee on Chemotherapeutic and Other Agents of the National Research Council, Keefer [54] stated that of 17 cases of bacterial endocarditis (organisms unspecified) treated with amounts from 250,000 to 1,760,000 units, over nine to 26 days, there were deaths in four, no appreciable effect in ten, and temporary improvement in three, of which two relapsed soon after stopping therapy. Later, Keefer [55] stated that of 55 treated cases only three were alive after one year of study. He mentioned other patients whose disease persisted after more than twenty million units of the drug.

The variations—indicated in the previously-mentioned tests—in susceptibility of different strains of *Streptococcus viridans* to penicillin, as to sulfapyridine, probably are a factor in the failures of penicillin. Acquired resistance to the action of penicillin, too, may perhaps be a second factor. Abraham and his co-workers [56] first demonstrated that organisms (*Staphylococcus aureus*) could be rendered fast to penicillin by growing them in broth with increasing amounts of the drug; Rammelkamp and Maxon [57] confirmed this, and showed that penicillin clinically may produce resistant strains, for

in four of 14 subjects, the *Staphylococcus aureus* isolated following treatment was much less sensitive to the drug than that cultured prior to it. These workers observed, significantly, that the development of penicillin fastness required prolonged exposure, contrasting with the readiness with which sulfonamide fastness results. Powell and Jamieson [58] found penicillin highly effective in mouse experiments against both parent and sulfapyridine-fast strains of pneumococci. Schmidt and Sesler [59] showed the converse: rendering pneumococci resistant to penicillin does not change their response to sulfapyridine. This absence of cross-resistance in either direction may hold important implications for future therapy of subacute bacterial endocarditis. These last authors produced penicillin fastness by serial passage of two strains of pneumococci through treated mice, and in one this persisted for 30 passages through normal mice; in vitro resistance accompanied that in vivo. McKee and Houck,[60] who developed fastness in hemolytic streptococci also and raised the resistance of staphylococci in vitro to 6,000 times that of the parent strain, found that penicillin-fast organisms show a proportionate decrease in virulence for mice—unlike sulfonamide-fast bacteria, which are unchanged in virulence. To Dawson and Hobby,[49] this finding makes penicillin-fastness much less significant; they regard clinical resistance as relatively rare, also, since it occurred in but one possible instance among their 100 cases, many given prolonged therapy. Certainly there was no suggestion of resistance in their patient whose temperature fell and cultures became negative on each of the many resumptions of penicillin; with sulfapyridine such repetitive responses are exceedingly rare.

As with the sulfonamide drugs, the mode of action of penicillin bears importantly on its effects in subacute streptococcal endocarditis. Most evidence indicates that it is bactericidal as well as bacteriostatic [47, 48, 61, 62]; unlike the sulfonamides, which reduce the rate of bacterial multiplication, penicillin causes an actual decrease in their number, an effect, moreover, not dependent on phagocytosis.[61] It has been shown, however,[48, 61] that the drug fails to sterilize cultures completely, and that 1 to 4 per cent of the organisms survive. Dubos [63] states: "When the susceptible organisms which have been exposed to the drug are transferred to a new medium free from it, they grow as readily as untreated cells." The growing out of such surviving organisms may account for the recurrence of active infection after withdrawal of penicillin.

The ability of penicillin to penetrate bacterial vegetations has not been investigated. Rammelkamp—who with Keefer [64] found that the drug failed to penetrate red blood cells in significant amounts (usually less than 10 per cent of the concentration in plasma)—believes that it does not penetrate the vegetations of subacute bacterial endocarditis (though it may enter the soft vegetations of the acute form).[65] To him, the presence of organisms in relatively avascular tissue is the chief obstacle to penicillin therapy in this disease.

In treating subacute bacterial (streptococcal) endocarditis with the sulfonamides and heparin, we found that if the chemotherapeutic agent could maintain a strong antibacterial effect, with sterilization of the blood and reduction of the temperature to normal or near it, during the period of decreased blood coagulability, recovery would result. If penicillin could produce a similar strong antibacterial effect, we believed that its use in place of a sulfonamide in the chemotherapy-heparin method might result in similar success. We began such treatment with the combination of penicillin and heparin on a patient with *Streptococcus viridans* endocarditis (table 2, case 10) on November 17, 1943. His temperature fell gradually to normal and the culture plates were cleared of bacterial growth; streptococci continued to appear in the broth, however, though they had become pleomorphic, poorly-staining, and strikingly reduced in size. Because of this failure to secure full antibacterial effect, sulfadiazine was also given, in the hope that the additive action would be effective. The patient received 1,900,000 units of penicillin, given during the first seven and one-half of the 10 days of heparinization, and a total of 23 grams of sulfadiazine administered during the last four days. After the use of sulfadiazine, blood cultures became negative in the broth as well as on the plates, and since the discontinuance of all therapy on November 27, the patient has been free of evidence of bacterial endocarditis and remains well and active.

Loewe and his associates have reported six cases of streptococcal endocarditis treated with apparent recovery by combined penicillin and heparin (table 1).[66] Their patients received from 1,400,000 to 7,890,340 units of penicillin, averaging 4,706,390 units, for periods of 13 to 51 days, with an average of approximately 31 days. In three of the patients, two, three, and four courses of treatment, respectively, were given because of continuing fever or positive blood cultures or both.

Much further experience is needed to determine the value of penicillin in subacute bacterial (streptococcal) endocarditis, and to learn its optimal dosage and plan of administration. It holds a clear advantage over sulfapyridine in its relative freedom from toxic effects (permitting high dosage), and its lesser tendency to induce bacterial resistance, but data are yet insufficient for comparing the two otherwise. In some cases, as in our own, a sulfonamide may valuably supplement its effect. Two questions in particular remain to be answered: Can penicillin, with its superiorities and its different mode of action, of itself result, unlike sulfapyridine, in a high proportion of successes in this disease? Is the accompanying use of heparin of real benefit with penicillin—which now seems likely—as it is with sulfapyridine?

Summary and Conclusions

1. In a large series of cases of subacute bacterial (streptococcal) endocarditis, sulfanilamide, sulfathiazole, and sulfadiazine at times gave transient

benefit, but resulted in no recoveries. Sulfapyridine reduced the fever in a majority and frequently rendered blood cultures negative, but cured only four of 197 patients. Neoarsphenamine, the sulfonamides together with intravenous typho-paratyphoid vaccine or with hyperthermia, and various other measures gave no lasting help.

2. Apparent recoveries from subacute streptococcal endocarditis reported since 1939 have been analyzed, and are listed in table 1. Because of their uncertainty, some cases reported as cured could not be included. A method of therapy is not fairly tested, it is pointed out, when the described technic has not been followed or is used with lack of care or persistency, and statistics based on such cases are misleading. Instances of endarteritis of the patent ductus arteriosus treated by surgical closure appear prominently in the list.

3. Sulfapyridine proved to be the most active of the drugs in lowering the temperature—not a mere "antipyretic" effect—and in rendering blood cultures negative—a sterilization of the blood stream—but its benefits passed off in a few days to two months. The failures of sulfapyridine to cure appear related to complications of the disease, toxic effects of the drug, its bacteriostatic rather than bactericidal mechanism, a low concentration of drug within the vegetations, its ineffectiveness against some strains of non-hemolytic streptococci, and the almost regular development of resistance to its action. Such clinical "escape" from sulfonamide effect after an earlier response has been shown to result from a decreased susceptibility of the bacteria themselves.

4. The author and White introduced heparin, in combination with chemotherapy in subacute bacterial endocarditis, in an attempt to prevent the further deposition of platelets and fibrin on the bacterial vegetations. The *combined* nature of this attack is again stressed; heparin has been beneficial only when sulfapyridine (or a related drug) reduced the temperature to normal or near it and sterilized the blood stream. Decreasing the blood coagulability during a period of such antibacterial effect has almost regularly resulted in recovery. Avoidance of the previous use of sulfapyridine, because of the readiness with which fastness develops, and the persistent continuance of treatment have been the two rules of success with this method. In addition to two in the original series, 10 further apparent recoveries from the disease treated by the author are noted (table 2).

5. Penicillin, effective in vitro against non-hemolytic streptococci, can reduce the temperature and sterilize the blood in cases of subacute bacterial (streptococcal) endocarditis, but on discontinuing the drug, fever and bacteremia have recurred in all but two of such patients (those of Dawson) reported to date. Lesser effectiveness of penicillin against some strains of the organisms, possible acquired bacterial resistance and inadequate penetration into the vegetations, and the failure of the drug (although bactericidal as well as bacteriostatic) completely to sterilize, appear as factors in its unsuccessful results.

6. Substituted for sulfapyridine in the heparin-chemotherapy method, penicillin was partially effective in a personally-treated case, but pleomorphic streptococci persisted on the culture plates; these disappeared with supplemental sulfadiazine, and the patient has remained well since completing the 10 day course of treatment in November 1943. Loewe's group has reported six apparent recoveries from streptococcal endocarditis with the use of penicillin and heparin. Penicillin excels sulfapyridine in its low toxicity and lesser tendency to induce drug fastness, but further data are needed to evaluate its effectiveness, to determine the best plan of therapy, and to learn if, unlike sulfapyridine, penicillin can alone result in a high proportion of successes, and if accompanying it also the use of heparin is advantageous.

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A CLINICAL STUDY OF RHEUMATIC PERITONITIS *

By HERBERT BERGER, M.D.† *Staten Island, New York*

THE appearance of four cases of rheumatic peritonitis at the Richmond Memorial Hospital recently served to bring attention to this infrequently discussed subject. Rheumatic fever causes inflammatory changes in and about the synovial membranes and it has long been known that other serous membranes may show similar involvement. Of these, pericardial disease is most common. Rheumatic pleuritis has been frequently described and is recognized clinically in many instances of acute rheumatic fever.

The occurrence of a similar reaction in the peritoneum coincidental with or preceding acute rheumatic fever has been suspected since 1635 when Ballonius [1] noted the occurrence of abdominal symptoms in rheumatism. Interest in this subject apparently waned for over 100 years and it was not until 1752 that Huxham [2] described the abdominal symptoms which precede or accompany rheumatic fever. In the past 15 years the condition has been noted and reported more frequently.[3]

An accurate estimation of the incidence of abdominal symptoms in rheumatic fever is not available because of a complexity of circumstances. Many of the abdominal symptoms are transitory and are deemed secondary to fever or to the salicylate therapy which is so widely used in this disease. Even when such patients are subjected to operation, the difficulty of differential diagnosis between rheumatic peritonitis and peritonitis of usual type, an acute surgical abdomen, persists. Since there is no typical microscopic rheumatic lesion in the peritoneum, even the pathologist examining appendices which have been removed at such operations, or examining blocks of peritoneal tissue removed at autopsy may fail to recognize the true etiological factor. Rhea [4] suggests that careful analysis of tissues from many locations in the peritoneum at necropsy of individuals dying from acute severe rheumatic fever will frequently show the presence of rheumatic peritonitis.

The gross and microscopic pathologic lesions of this condition have been studied by several investigators. Felson [5] has noted actual ileal lesions in an individual dying from rheumatic fever. These were ulcers that penetrated from the mucosa to the peritoneum. This finding suggests that some of the abdominal symptoms noted in rheumatic fever may have been due to lesions within the intestinal wall as well as on its peritoneal surface. Diffuse hemorrhagic changes have been described by Colleyes [6] in the intestinal wall

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From the Medical Service of the Richmond Memorial Hospital.
† Surgeon, U.S.P.H.S. (R).
Approved for publication by Thomas Parran, Surgeon General, United States Public Health Service.

of patients with rheumatic fever. Friedberg and Gross [7] noted abdominal symptoms in active rheumatic heart disease. On later study, these proved to have been caused by periarteritis nodosa. The authors conclude that there is a close relationship between mesenteric periarteritis nodosa and rheumatic vascular disease. In a later communication Felson [8] suggests that the lymphoid tissue of the intestinal tract tends to "drain out the infectious agents in many diseases and thereby causes abdominal pathology and symptoms to appear." Aschoff-like bodies have been described by Paul [9] in sections of the diaphragm and from various other parts of the upper abdominal peritoneum. His patient had few striking abdominal signs or symptoms in life. Perihepatitis was noted at autopsy in fatal cases of rheumatic fever by Lenoble and Pineau,[10] Poynton,[11] Libman,[12] and Pierson.[13] However, necropsy studies do not give a true index of the frequency of this condition, for positive findings are not noted on postmortem examinations except in those instances in which the individual succumbs to an acute attack of rheumatic fever while the abdominal symptoms are present. Since this combination of events rarely occurs, Rally's [14] report of 140 cases of serositis in 3,500 autopsies of individuals dying of rheumatic fever does not offer an accurate picture of the actual incidence of this condition.

The present study is largely a clinical one and was undertaken after the observation of four patients whose presenting symptoms were abdominal in character and who, consequently, offered a problem in diagnosis.

The abdominal symptoms of rheumatic fever have been divided by Barraldi [15] into three groups. First the digestive, second the pseudo-appendiceal, and third, the peritoneal. It is to be emphasized that these symptoms may precede, occur concomitantly with, or follow other manifestations of rheumatic fever. It is even possible that abdominal infection may be the only evidence of an attack of rheumatic fever. This hypothesis may partially serve to explain the origin of those cases of rheumatic heart disease in which a history of arthritic, choreic, or other more frequently recognized manifestations of rheumatic fever can not be elicited. The greatest diagnostic problem occurs in those instances in which the peritoneal symptoms precede the development of joint or cardiac disease. In such cases the patient may present a series of signs and symptoms which are almost indistinguishable from those caused by acute inflammatory abdominal conditions, particularly acute appendicitis. The difficulties involved might best be illustrated by the case reports.

Case Reports

Case 1. R. M., 12 year old white male, complained of acute abdominal pain of 20 hours' duration when first seen at 5 p.m. on July 10, 1941. He had been nauseated but had not vomited. The symptoms had started with pain in the abdomen which was localized rather indefinitely in the lower abdomen. The patient could not say whether the right or left side was most uncomfortable. Temperature had been elevated since early that morning (100.2° F.–38.8° C. at 10 a.m.) and on examination was 104.2° F. (41.1° C.).

On examination he was acutely ill and greatly distressed. The entire abdomen was tender and rigid. The rebound phenomenon was present. Urine was normal. Blood count showed 13,200 leukocytes, 76 per cent of which were polymorphonuclear and 13 per cent of these were immature forms. The red blood count was 3,620,000, the hemoglobin 9.8 grams. A diagnosis of peritonitis, probably secondary to acute appendicitis, was made. At laparotomy (at 9 p.m.) the entire peritoneum was edematous and injected. The smaller blood vessels on the peritoneal surface of the mesentery and the intestine were clearly visible. The appendicular peritoneal surface was involved but, not more severely than the adjacent ileum or parietal peritoneum. There was no free pus in the abdomen. The spleen and liver were both rather large and soft. The appendix was removed and the postoperative diagnosis was "hematogenous peritonitis," organism to be investigated. Pending the identification of the offending organism in the peritoneum, chemotherapy in the form of sulfathiazole was instituted empirically. During the first 24 hours, 12 grams (180 grains) were administered rectally. On subsequent days 6 grams (90 grains) were administered daily by mouth. The concentration of sulfathiazole in the blood was not determined. Under this régime the temperature dropped gradually to 98.6° F. on July 16. The sulfathiazole was discontinued on July 17, and the patient was discharged on July 23 as recovered.

The pathological report of his appendix is as follows: "The organ is 9 centimeters in length, the serosal surface is smooth, and the vessels of the serosa are injected. The lumen is patent. On microscopic study, the mucous membrane is intact. There are many dilated capillaries filled with blood. There are many lymphocytes and polymorphonuclear leukocytes in the subperitoneal area."

It is interesting that the child had been under constant surveyance since infancy, yet never had any cardiac murmurs or evidence of rheumatic disease of the heart, joints, or tendons manifested themselves. He was a rather "nervous" child, but, as this was a familial trait, it is doubtful whether he ever had had chorea. The tonsils had been removed four years previously.

The culture taken from the abdomen yielded no growth and during his stay at the hospital, despite persistent search, no focus was found which may have excited the peritonitis. It was assumed, therefore, that the origin of his condition was probably pharyngogenic. On July 24, the day after his discharge, the original symptoms reappeared with abdominal pain and fever reaching 103.2° F. (39.6° C.). He was nauseated and vomited on two occasions. General examination again revealed only abdominal signs: general tenderness, retraction of the abdomen and rigidity. Sulfathiazole therapy was reinstituted and 6 grams (90 grains) were administered daily. The drug was continued for five days, during which period the temperature curve was not influenced at all. It was then discontinued since it was felt that the drug, if it were to be effective at all, should have caused some change in the condition after this period of time. Secondly, the drug itself may have been the cause of the continued pyrexia. Only on July 28 did the true nature of this disease begin to disclose itself with the appearance of several tender and painful nodules on the extensor surfaces of both legs and about the right elbow. These lesions may have been toxic manifestations of sulfathiazole therapy, or they may have been rheumatic nodules. However, when swelling, pain, redness and heat developed in the right ankle on July 31, followed by a similar condition in the left knee three days later, it seemed that the disease could safely be diagnosed rheumatic fever. Sodium salicylate, 4 grams (60 grains) per day, was administered with 0.6 gram (10 grains) of sodium bicarbonate on August 3 and daily thereafter. Although the left shoulder became inflamed on August 6, symptoms all disappeared by August 8. The temperature dropped rapidly in two days to 99° F. (37.2° C.) and continued between 98° F.

(36.6° C.) and 100° F. (37.7° C.) until August 17. The abdominal symptoms disappeared after one day of this therapeutic régime. A systolic murmur was first heard at the apex on August 5 and again on August 8 but was not heard again. Sedimentation rate on August 3 was 45 mm. in one hour. This became normal on October 1 when the child was finally permitted out of bed. There were no residual signs or symptoms. That sulfathiazole intoxication did not cause the joint manifestations, nodules and fever was indicated the following spring when the child developed lobar pneumonia. He was treated with full doses of this drug and recovered rapidly with no allergic phenomena.

Case 2. E. DeF., age 10, female, was admitted to the hospital on February 26, 1942, with a history of severe abdominal pain associated with nausea, vomiting and fever. The pyrexia had appeared four days earlier. The parent believed the condition to be a "cold in the stomach" and had treated her at home with hot applications to the abdomen, hot drinks by mouth, ice to the head and hot mustard foot baths. During this period the condition became worse until she finally sought medical advice.

The family history in this case was interesting and, as the author has taken care of this family for the past seven years, he was able personally to verify some of the unusual features. The father had always been well and had no cardiac symptoms. The mother lost both her parents at an early age, under 40. Both died suddenly while apparently in good health. The maternal grandparents had eight children. Five of these died suddenly while apparently in good health. The writer had examined several of these patients prior to their death, and the entire family lived in constant dread of sudden exitus. Two of those examined before death were entirely normal on clinical, radiographic and cardiographic study. The mother, however, had rheumatic heart disease, Class 1–A. There was no cardiac disease in the patient's siblings (two sisters and one brother).

The past history of this patient revealed an attack of acute catarrhal jaundice two years before. There were no other pertinent past illnesses.

On examination the temperature was 102.2° F. (39° C.), the pulse 120, respirations 20. She was acutely ill. The legs were drawn up. The abdomen was retracted and very tender. Rigidity was present throughout. A systolic murmur was present at the apex, which had not been present two years previously on the last examination. The blood count showed white blood cells 9,200, 84 per cent polymorphonuclears, of which 12 per cent were immature. The urine was clear. Red blood count was 3,800,000 with 8.5 grams of hemoglobin. The differential diagnosis lay between rheumatic peritonitis, suggested by her familial cardiac history, and an acute purulent peritonitis. Since operation was believed to be premature even if this were a diffuse purulent peritonitis because of the need of awaiting localization, laparotomy was deferred. During this period of observation, salicylate therapy was instituted to aid in therapeutic differentiation. Therefore, 4 grams (60 grains) of sodium salicylate and 1 gram (15 grains) of sodium bicarbonate were given daily. On February 27 there was much less abdominal pain. Tenderness and rigidity had fairly well disappeared, and the temperature was 101.4° F. (38.5° C.). This treatment was continued for two months, during which time the temperature dropped slowly to normal, hovering about 99° F. (37.2° C.) to 100° F. (37.7° C.) for over a month. A diastolic apical murmur appeared which was still present on the last examination June 4, 1942. Sedimentation rate on February 28 was 62 millimeters and was normal on June 4. The heart was examined fluoroscopically on June 8 and a straight left border was seen such as is commonly associated with mitral valvular disease. The final diagnosis: acute rheumatic fever, first manifesting itself as rheumatic peritonitis, complicated by carditis, mitral insufficiency and stenosis, regular sinus rhythm.

Case 3. R. S., age 10, male, was admitted to the hospital April 9, 1942, complaining of pain in the abdomen. On April 2 he had had a sore throat, with a temperature of 101.6° F. (38.6° C.). Sulfathiazole was given prior to admission, but the amount is not known. On April 5 large hives appeared on the skin of the abdomen and extremities and on April 6 pain appeared in the abdomen. There was no nausea and no vomiting, but anorexia was marked. The past and family histories were inconsequential.

On examination he was acutely ill. The respirations were not labored. The temperature was 102.2° F. (39° C.), pulse 120, respirations 28. The abdomen was splinted during respiration. A macular rash was noted on the arms and trunk. The lips were dry, the tongue coated and leathery. The heart was normal. The lungs were clear. The abdomen was rigid in the upper half and slightly looser in the lower half, particularly in the appendicular area. Clinical diagnosis was peritonitis of undetermined origin, probably not related to appendicitis. The urine was normal. The white blood count was 10,400, 86 per cent polymorphonuclear cells, of which 14 per cent were immature. There were 9.8 grams hemoglobin and the red blood count was 4,250,000. The Wassermann reaction was negative; sedimentation rate 160 millimeters in one hour (Westergren). Stool culture was negative. Agglutination tests for typhoid, paratyphoid and typhus were all negative. Consultation with the surgical staff was held, and it was felt that the child was too acutely ill to permit surgical intervention. It was deemed wiser to await localization. On the possibility that this might be rheumatic peritonitis, salicylate therapy was instituted at once and on April 10, 1942 the abdomen was much softer. The child seemed less seriously ill, although he was somewhat confused. The dosage was 4 grams (60 grains) per day with sodium bicarbonate 1 gram (15 grains), and on April 11 the temperature reached 99° F. (37.2° C.) at which level it remained for several days. On April 18 a systolic murmur was heard over the apex and transmitted to the axilla and a localized pericardial friction rub was heard at the apex. The abdomen was no longer retracted or tender. Roentgenographic examination on admission showed no cardiac or pulmonary abnormality. The electrocardiogram on April 27 was suggestive of pericardial change because of elevation of the ST segments in all standard leads. This elevation persisted on two subsequent studies at one month intervals. At this time, April 28, a diastolic murmur was first heard at the mitral area. The pericardial friction rub was heard for only two days. The temperature was normal on April 29, and a roentgenogram at this time revealed some straightening of the left cardiac border. Despite continued salicylate therapy, the temperature rose on May 2 to 100.4° F. (38° C.) and persisted in this neighborhood until his discharge on July 10, 1942. The sedimentation rate during the entire hospital stay continued high. On April 28 it was 69 millimeters, on May 30 it was 73, on June 27 it was 73 mm. in one hour. During this admission a diastolic aortic murmur was never heard, but the diastolic pressure dropped steadily, reaching a level of 35 mm. of mercury on June 15. He was discharged at the request of his parents. He continued to receive salicylates while at home.

The patient was readmitted to the hospital on January 2, 1943. At this time he had all of the peripheral vascular phenomena of aortic insufficiency and a diastolic aortic murmur could easily be distinguished. The cardiac silhouette had increased in size and the general condition was considerably worse than on the first admission. The child was again taken home on January 21 in care of his family who were very coöperative and administered excellent convalescent care. Low grade fever persisted throughout the admission in January and continued as well at home. The cardiogram during the second admission revealed a prolongation of the PR interval to .26 second. Blood cultures taken both in the hospital and at home were sterile. Fluoroscopy on January 20, 1943, showed marked enlargement of the left auricle and

the left ventricle. While at home he continued in poor condition and died on February 12, 1943 in congestive failure. Autopsy was not permitted.

Case 4. V. M., age 37, female, was first examined on April 15, 1942. She complained of severe abdominal pain, fever and nausea.

Past history included a biopsy of a mass in the breast in 1938 which proved to be a fibroma and one normal pregnancy in January, 1942. There were no unusual postpartum sequelae. Aside from ulcerative colitis in her mother, the family history was not significant. There were no siblings. Her husband was living and well.

The patient complained of abdominal pain which started three days prior to examination as a vague discomfort in the umbilical area which gradually spread throughout the abdomen. She was moderately nauseated, but did not vomit until April 15, 1942, just prior to examination. The temperature had not been taken until April 14 when it was 101° F. (38.2° C.).

Examination revealed an acutely ill female, temperature 103.6° F. (39.7° C.), pulse 144, respirations 22. The legs were drawn up and the abdomen retracted. The abdomen did not move during respiration. General examination was negative except for the abdomen which showed marked rigidity and great tenderness throughout. The heart was normal and had been normal on many examinations during the past eight years. Laboratory studies revealed red blood cells 3,210,000, hemoglobin 7.8 grams, white blood cells 10,200, polymorphonuclears 76 per cent of which 12 were immature. Urine was normal. It was assumed that this patient had generalized peritonitis from some unknown cause and since it seemed wise to await the localization of symptoms before attempting any surgical intervention, she was treated empirically with sulfadiazine 2 grams (30 grains) immediately and 1 gram (15 grains) every four hours. Morphine was given for relief of abdominal pain. The temperature gradually dropped to 102° F. in three days and remained there despite sulfadiazine levels of 18 milligrams per cent for four additional days. The abdomen was still tender throughout, but the rigidity was less marked. The patient did not look so alarmingly ill. However, since the temperature was not septic in type and localizing signs could not be found, it did not seem that an intra-abdominal abscess was developing. Sulfadiazine was stopped and salicylate therapy was instituted on April 22, 6 grams (90 grains), per day with sodium bicarbonate. The temperature dropped in two days to 99° F. (37.2° C.) and stayed between 99 and 100° F. (37.2–37.7° C.) for some time. The patient felt well. Abdominal pain had practically disappeared, as did all the objective findings. It seems that this too might have been an instance of rheumatic peritonitis. However, nothing in the history or physical signs thus far served to prove this diagnosis. The sedimentation rate was 88 mm. on April 22 and this dropped to 52 mm. two weeks later. The heart was examined frequently but no abnormality was noted. Salicylate therapy grams 4 (grains 60) per day was continued with sodium bicarbonate. The temperature did not become normal and the sedimentation rate continued between 45 and 60 mm. per hour. On May 20 a systolic murmur was heard at the apex and was constantly present thereafter. On May 26 murmurs were heard both at the apex and the base. The patient was quite pale. The blood count at that time showed 2,750,000 red blood cells and 56 per cent hemoglobin. The spleen was palpable; blood culture was sterile. However, subsequent cultures showed *Streptococcus viridans* one week later and despite intensive sulfadiazine therapy, no reversal in the blood culture was obtained. She continued to receive numerous transfusions and intravenous sodium sulfadiazine regularly, keeping the blood level of the drug between 15 and 20 mg. per cent constantly. She continued to fail and died on October 5, 1942. Autopsy could not be obtained.

Final diagnosis was apparently acute rheumatic fever, first manifesting itself as rheumatic peritonitis complicated by subacute bacterial endocarditis.

Discussion

This investigation is purely clinical, as there is no laboratory proof of the diagnosis in any of these cases. However, several facts do stand critical examination,

1. The abdominal signs and symptoms subsided during the administration of salicylates and bicarbonate in large doses and did not respond to chemotherapy with the sulfonamides.

2. In each case subjective and objective abdominal disease preceded either definite clinically recognizable acute rheumatic fever, rheumatic heart disease or subacute bacterial endocarditis.

3. No patient had had rheumatic fever or rheumatic heart disease prior to the onset of the seizure described. One patient had a significant cardiovascular family history.

4. A generalized peritoneal inflammation was observed clinically in the one case subjected to laparotomy. This case developed typical acute rheumatic fever later.

5. In Case 4, the abdominal symptoms may have been embolic manifestations of subacute bacterial endocarditis appearing in a previously damaged heart. Several facts are against this possibility. This young woman never showed any signs of rheumatic or congenital heart disease. She had never had any subjective or objective cardiac abnormality on any of the previous examinations by several physicians. On her two hospital admissions, she was examined by the resident physician and by the anesthetist and no record of cardiac abnormality was noted on either chart. She believed firmly in regular physical examinations and the records over eight years show no preexisting cardiac disease. She had been fluoroscoped on several of these examinations and the cardiac silhouette was recorded as normal. She had weathered her first pregnancy at the age of 37, just three months before the onset of symptoms, with no evidence of vascular difficulty. During her prenatal period she was examined regularly by an obstetrician who found no cardiac disease. No embolic phenomena appeared anywhere in her body during the period of abdominal complaints. Again, these facts fail to prove that she did not have preëxisting subclinical cardiac disease, but they do weigh against that assumption.

Conclusions

1. Generalized peritonitis may be rheumatic in origin.

2. In instances of abdominal disease in which clinical study points toward the diagnosis of diffuse peritonitis, the treatment of choice is usually conservative and non-operative. A therapeutic test in the form of large doses of salicylates with bicarbonate may be safely attempted in such cases to aid in the diagnosis of this disease. Such patients, however, must not exhibit a septic temperature, a mass in some abdominal area, or tenderness or rebound tenderness constantly referred to one area such as McBurney's point.

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CASE REPORTS

THE SYNDROME OF PRECOCIOUS PUBERTY, FIBROCYSTIC BONE DISEASE AND PIGMENTATION OF THE SKIN: ELEVEN YEARS' OBSERVATION OF A CASE*

By Bernard M. Scholder, Lieut. Comdr. (M.C.), U.S.N.R.,
Mount Vernon, New York

In 1922 Weil [1] first described the syndrome of precocious puberty, fibrocystic bone disease and pigmentation of the skin. Since then there have been reports of some 18 cases.[2, 3, 4, 5, 6, 7, 8, 9, 10, 11, 12, 13, 14] These are presented in table 1. Although the syndrome is interesting because it is uncommon and bizarre, its chief appeal arises from attempts to explain the various phenomena in the light of present day knowledge of neuro-endocrine mechanisms.

The patient to be presented has been under constant medical scrutiny since the onset of symptoms at the age of three, and has been under the author's care for 11 years.

Case Report

The patient is a 19 year old young lady who first came under observation at the age of eight.

The history revealed that she was the second born child and that her delivery was attended by considerable trauma to the mother.

The child developed well in the first three years. The only illness which occurred during this time was chicken pox. At the age of three, however, vaginal bleeding suddenly appeared; this recurred at irregular intervals during the fourth and fifth years, gradually tapering off. At seven years of age it recurred, and since then has been a constant feature. In character the vaginal bleeding exhibited periods of metrorrhagia and amenorrhea, but during the last two years has tended to be fairly regular. Breast tenderness was present with the onset of the menses at age three, and at the age of four prominence of the breasts was first noted. At the age of five pubic hair appeared and asymmetry of the face became apparent.

When the patient was six years old, she sustained a fracture of the left humerus and in the roentgenograms taken at this time abnormalities of the bones were first brought to light.

Some time between the onset of the menses and the fracture of the humerus a small area of pigmentation appeared over the left lumbosacral region.

When the patient was nine years of age she was studied in the consultation service of Mt. Sinai Hospital in New York, where the essential findings were as follows: Asymmetry of the face in the region of the right maxilla and the right eye, marked breast development, pubic hair and peculiar gait. Roentgen-ray studies revealed multiple areas of bone absorption in the left upper and lower extremities and

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The opinions and assertions contained herein are those of the writer and are not to be construed as official or reflecting the views of the Navy Department or of the Naval Service at large.

left ilium. The right side of the skull revealed bone condensation at the base and about the right orbit. A biopsy taken from the left humerus revealed fibrous osteitis. Calcium and phosphorus determinations were within normal limits. At this time also she was seen by Dr. Robert T. Frank, who had seen her previously at the age of seven. He made the observation that the vulva and internal organs were small and infantile for a patient who had been menstruating since the age of three. Studies of sex hormone in the urine revealed an increase in the amount which is found in children of her age.

TABLE I

Year	Author	Age of Patient	Precocity	Skeletal Changes	Pigmentation	Remarks
1922	Weil	9	Menstruation since infancy	Spontaneous fracture 18 mos.	Abnormally pigmented skin	Sclerae blue
1932	Gaupp	8	3 yrs. breast development, pubic hair, menstruation	2 yrs. limp; 3–5 yrs. fractures	Not stated	Bones showed osteitis fibrosa; normal parathyroids, ⅓ removed
		9	9 yrs. menses, breast, genital development	2 yrs. rickets; 6 yrs. bow legs, fractures	Pigmented mole	Neck explored; no parathyroid tissue identified
	Freedman	14 mos.	4 mos. menses, genital development	3 yrs. fracture	6 mos. brown pigmented areas	Laparotomy for adrenal tumor: none found; small ovarian cyst
1933	Stalmann	8	9 mos. menses	5 yrs. osteitis fibrosa-fractures	Birth-pigmented patches of skin	
	Snapper and Parisel	10	7 yrs. menses	7–9 yrs. fractures	Brown nevi	Surgical exploration neck; no parathyroid tumors found
1934	Goldhamer	9	2 yrs. menses	3 yrs. tumor jaw; 5 yrs. fracture	Nevi	
1936–1937	McCune and Bruch	10	2 yrs. menses, breasts, hair developed	1 yr. bowing of legs; 3½ yrs. fractures	2 yrs. brown patches in skin	Neck explored, no parathyroid tumors found; bone showed osteitis fibrosa
	Albright Butler Hampton Smith	23	7 yrs. menses	8 yrs. fractures	Brown spots	
		39	1 yr. menses	10 yrs. fracture	Brown spots	
		8	3½ yrs. menses	Seen in x-rays	Brown patches	Bone biopsy: osteitis fibrosa

TABLE I—*Continued*

Year	Author	Age of Patient	Precocity	Skeletal Changes	Pigmentation	Remarks
1938	Mondor Ducroquet Leger Laurence	14	7 yrs. menses	7 yrs. fractures	Since birth	
1939 Jan.	Summerfeldt and Brown	10	3 yrs. menses; 5 yrs. breasts and pubic hair	3 yrs. waddling gait; bone cysts. 6 yrs. fractures	12 mos.	Dense skull bones. No parathyroid tumor found
		6	2 yrs. menses; 6 yrs. breasts and pubic hair	2 yrs. limp; osteoporosis, fracture at 6 yrs.	4 mos.	Thickened base of skull
1939 Feb.	Robson and Todd	33	Breasts, pubic hair at 6 yrs.; menses at 7 yrs.	7 yrs. limp, fractures	At 33	At 4 grew unusually; at 33 neck explored: no parathyroid tumor found
1939 Sept.	F. Braid	2½	2½ yrs. menses	1½ yrs. fractures; bones abnormal	3 mos.	
1940	Diez	18	5 yrs. menses, breasts and genital development	5 yrs. limp, fractures		At 10 biopsy of bone, parathyroids explored, negative findings
1944	Dockerty, Meyerding and Wallace	35	7 yrs. menses	7 yrs. limp; 34 yrs. fracture	At birth	Bone biopsy: osteitis fibrosa; ovarian cyst

The conclusions reached at this time were that the patient had a "complicated endocrine disease, involving the parathyroid, suprarenal cortex and ovarian-pituitary functions. The disturbance in parathyroid function is evident from the marked rarefaction of the long bones and the tendency to fracture. It is not contraindicated by the finding of a normal blood calcium and phosphorus. It is supported by the microscopic study of the bone which is reported as showing evidence of an osteitis fibrosa. The pituitary, suprarenal cortex, ovarian syndrome is suggested by the precocious development of the breasts, pubic hair and onset of menstruation at age three. An intravenous pyelogram failed to reveal any evidence to support the possibility of a tumor of the adrenal cortex."

From this time on the patient developed nicely, increasing in height and weight until the age of 12 when she reached her maximum height. (This was subsequently discovered to be due to early closure of the epiphyses.)

At the age of 10, the patient began to suffer with vernal conjunctivitis and hay fever which were ameliorated by pollen injections.

Her menstrual periods continued in irregular fashion for some time and were characterized by long intervals, followed by periods of metrorrhagia. At the age of 12 the patient was given a course of injections with antuitrin-S, the purpose of which was to stimulate maturation of ovarian follicles and thus establish more

regularity. Following this course of treatment the menstrual cycle was much more normal.

At the age of fifteen the patient sustained a fracture of the left radius, following a fall. The interesting features of this condition were that the fracture line was very fine, it ran through a cystic bone area, there was no displacement, but the pain was remarkably intense,—out of all proportion to the physical or roentgenographic findings.

Intellectually the patient has developed most satisfactorily, her scholastic attainments being of the highest order. In her relations with older people she impressed one as being quite mature.

At the present time the patient is completing her second year in college studies.

FIG. 1. The patient in 1937, 12 years of age. Note the asymmetry of the face due to a bulge in the right frontal bone, and the right maxilla. The right eye is lower than the left. Compare with figure 3, a postero-anterior roentgenogram of the skull.

always having achieved top ranking in her classes. She is active and vivacious, and her general appearance, outside of the mild limp and asymmetry of the face, gives no clue to the profound changes which have taken place and to the long history of these changes.

Physical Examination. Physical examination at the present time shows a well developed, well nourished girl, 61.5 inches tall and weighing 110 pounds. There is an asymmetry of the face due to a marked prominence of the right frontal and maxillary bones. The right eyeball is lower than the left (figure 1). There is obstruction in the right nostril due to deviation of the septum (to the right) with a projecting spur making contact with the right inferior turbinate bone. The middle turbinate shows cystic degeneration. The dentition is normal and the prominence of the right maxilla is seen above the right upper teeth. The thyroid isthmus is palpable:

the heart, lungs and abdomen show no abnormalities. The breasts are prominent. The genital organs appear to be about normal in size and a normal female escutcheon is present. The left upper and lower extremities are thinner than the right. There is a lumbar scoliosis to the left with a tilt of the pelvis and an apparent shortening of the left lower extremity. There is an area of yellowish brown pigmentation about 4 cm. in diameter in the skin overlying the left lumbosacral joint.

Laboratory Findings. Laboratory studies have been done over the past 10 years and are summarized herewith:

I. Blood

(*a*) Count (1934) Hemoglobin 12 gm., red blood cells 5.5 million; white blood cells 8200, of which 51 per cent were polynuclear leukocytes, 48 per cent were lymphocytes and 1 per cent eosinophiles.

(1936) Hemoglobin 10.5 gm., red blood cells 5 million; white blood cells 6800 with 34 per cent polynuclear leukocytes, 56 per cent lymphocytes, 7 per cent monocytes and 3 per cent eosinophiles.

(*b*) Sedimentation rate (1934) normal

(*c*) Kahn test (1934) negative

(*d*) Cholesterol (1934) total 230 mg. per 100 c.c.
(1934) 215 mg. per 100 c.c.
(1936) 152 mg. per 100 c.c.

(*e*) Calcium (1934) 10.8 and 11.2 mg. per 100 c.c.
(1936) 12.7 mg. per 100 c.c.
(1942) 12.3 mg. per 100 c.c.

(*f*) Phosphorus (1934) 5.0 and 4.7 mg. per 100 c.c.
(1936) 3.6 mg. per 100 c.c.
(1942) 3.5 mg. per 100 c.c.

(*g*) Phosphatase (1942) normal

(*h*) Hamilton test (1942) negative

II. Urine (1934), (1936), (1942) within normal limits

III. Basal metabolic rate
(1934) minus 9
(1937) minus 4

IV. Bone histology (reported by Dr. Paul Klemperer, Mt. Sinai Hospital) (figure 2). Microscopic sections of one fragment of bone revealed bone trabeculae of unusual breadth and a conspicuous fibrillar structure. Between these bone trabeculae there is a cellular connective tissue apparently substituting the normal bone marrow. This tissue shows a uniform formation by fibroblasts and does not reveal any granulomatous areas. Sporadic osteoclasts are seen. In a second fragment the greater portion of the section was formed by a dense connective tissue within which metaplastic bone formation was seen. The microscopic findings are those of fibrous osteitis.

V. Roentgen findings. The roentgenographic findings in the skeleton are striking. In the skull (figures 3 and 4) areas of bone condensation are seen in the right frontal and maxillary areas with reduction in size of the right orbit. The lateral view shows marked condensation of the base in the anterior and middle fossae areas. Figure 5 shows areas of marked bone absorption in the left humerus and scapula; the epiphyses in the proximal ends of the humeri are almost completely closed. The bone biopsy seen in figure 2 was taken from the left humerus. Figures 6, 7 and 8 show areas

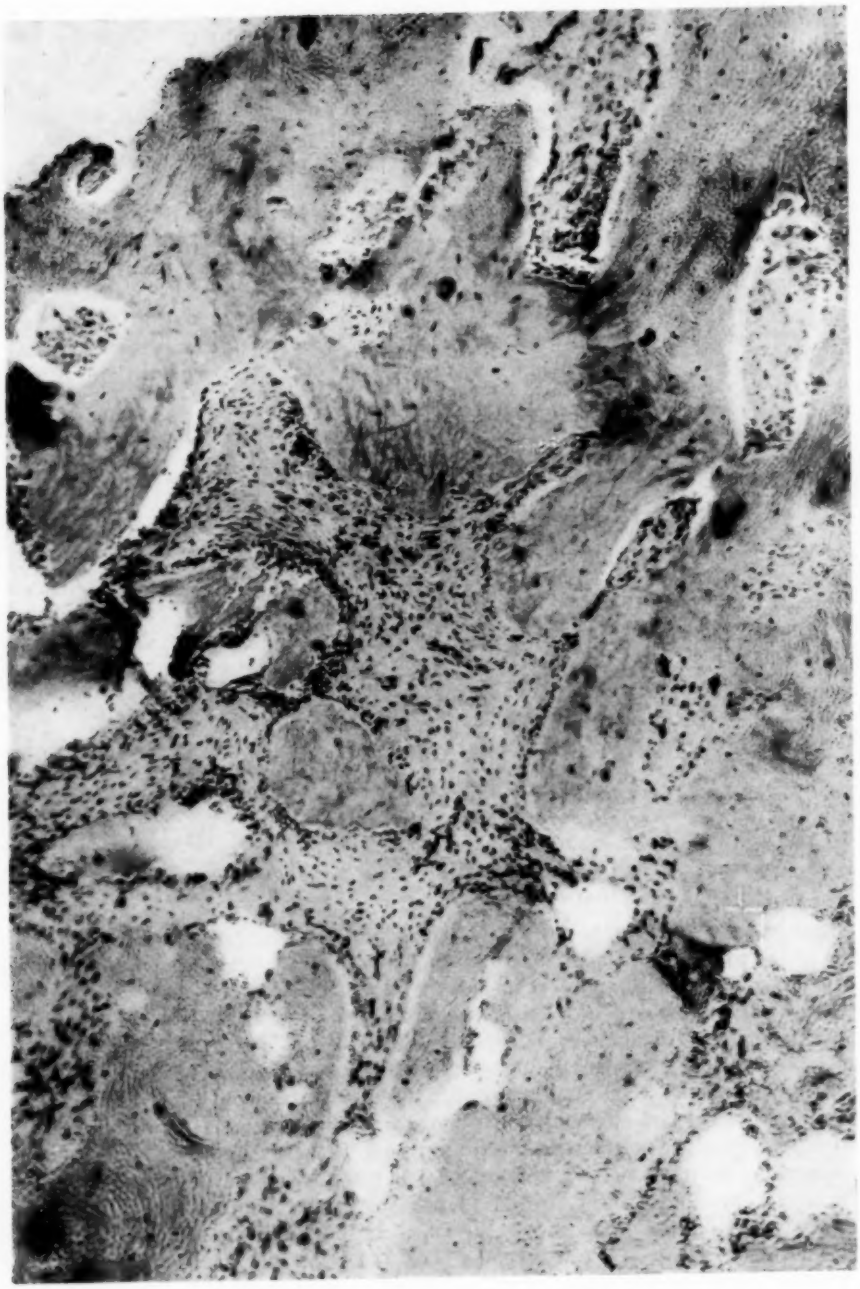

FIG. 2. Section of bone from the left humerus, at the site of the fracture when the patient was 6 years old; specimen taken in 1934 at Mt. Sinai Hospital, New York, shows thickening of bony trabeculae and replacement of marrow by fibrous tissue. (Courtesy Dr. Paul Klemperer, Mt. Sinai Hospital, New York.)

of bone absorption in the left forearm, left pelvis, left femur and left tibia. In addition the closure of the epiphyses is well seen.

The roentgenograms reproduced were taken in 1937 when the patient was 12 years of age. The characteristics were (1) Involvement of right side of skull and left side of torso and extremities; (2) bone condensation in skull and bone absorption in trunk and extremities; (3) early maturation of skeleton.

FIG. 3. Postero-anterior view of skull showing density of bones on the right side and narrowing of right orbit. (An idea of the density of the bone may be obtained from the fact that in 1935 an attempt was made to give the patient more room in the right nasal fossa; only a few small pieces could be removed, and in doing so the operator broke his instrument.)

SUMMARY OF FINDINGS

Thus, it is seen that our patient presents the cardinal symptoms of an endocrine syndrome characterized by precocious puberty, fibrocystic bone changes and pigmentation of the skin.

The syndrome has been compatible in our patient with an otherwise normal life and development. The externally visible features have been slight asymmetry of the face, a mild limp and short stature—growth having stopped at the age of twelve when our patient reached her maximum height of 61.5 inches.

Laboratory studies revealed an increase in the amount of sex hormone in the urine for the age at which it was studied (nine years). Blood chemical studies have

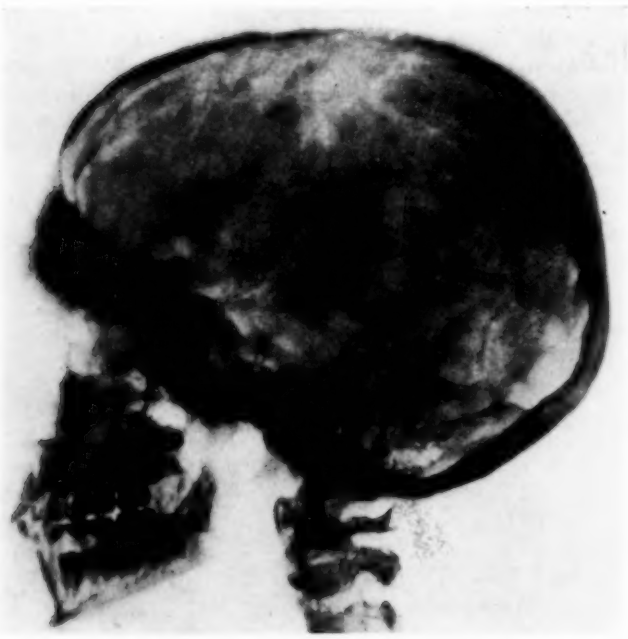

FIG. 4. Lateral view of the skull showing density of the bone at the base; the sella turcica shows no abnormalities.

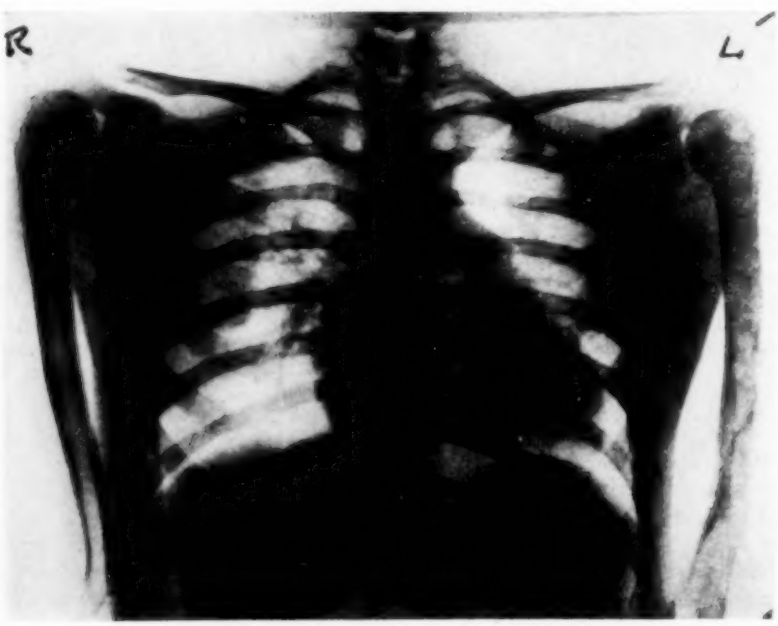

FIG. 5. Showing areas of bone absorption in the left humerus and left scapula. The epiphyses are closed. The bone biopsy shown in figure 2 was taken from the left humerus.

been within normal limits. Roentgenographic studies have shown profound and widespread changes, with slight progression of the findings in 10 years.

The only factor of possible significance in the patient's history is that her birth was extremely difficult, occasioning considerable trauma to the mother. This could conceivably have caused some damage to the central nervous system which became apparent in the unfolding of the patient's clinical condition.

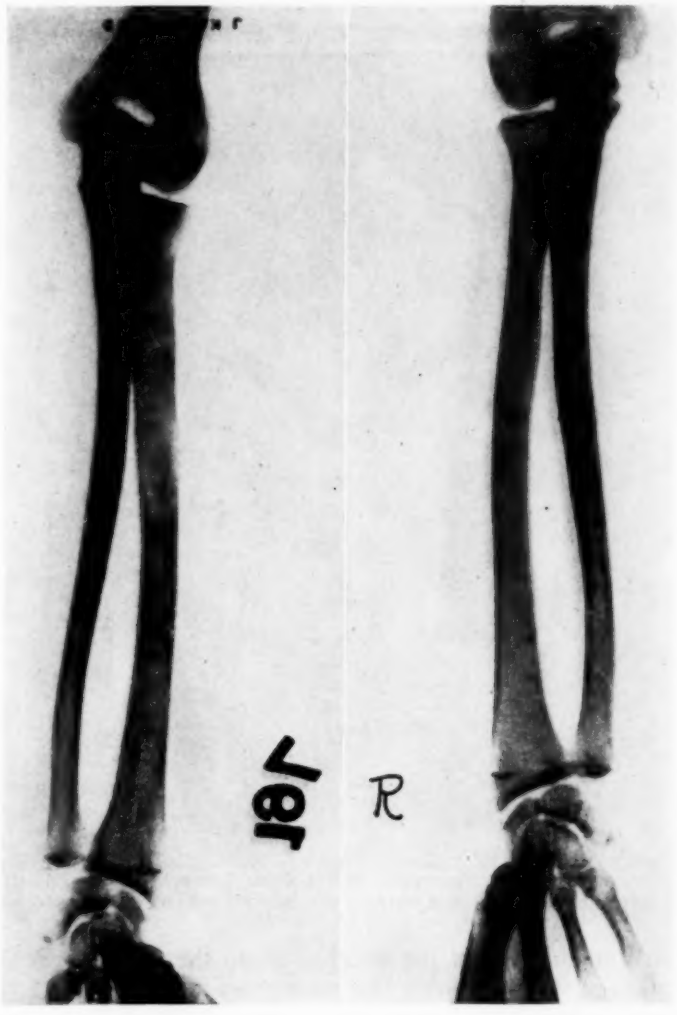

FIG. 6. Showing areas of bone absorption in left radius; the epiphyses are closed.

DISCUSSION OF THE SYNDROME

The remarkable skeletal changes which have been described in this syndrome have served to focus most of the attention on this feature; for this reason the early reports of these cases have been found under various titles indicating the skeletal changes.

However, careful analysis of the facts in the 19 cases thus far presented (including author's case) reveals that in only two instances were the skeletal changes first to appear. The precocious puberty was the presenting feature in 12, and skin pigmentation was first in five. In view of these facts, it would seem to be more fruitful to limit discussion of this syndrome to those cases showing precocious puberty and bone changes, and not to include the males who *do not* show any evidence of *precocity;* in fact, the reports of cases in males do

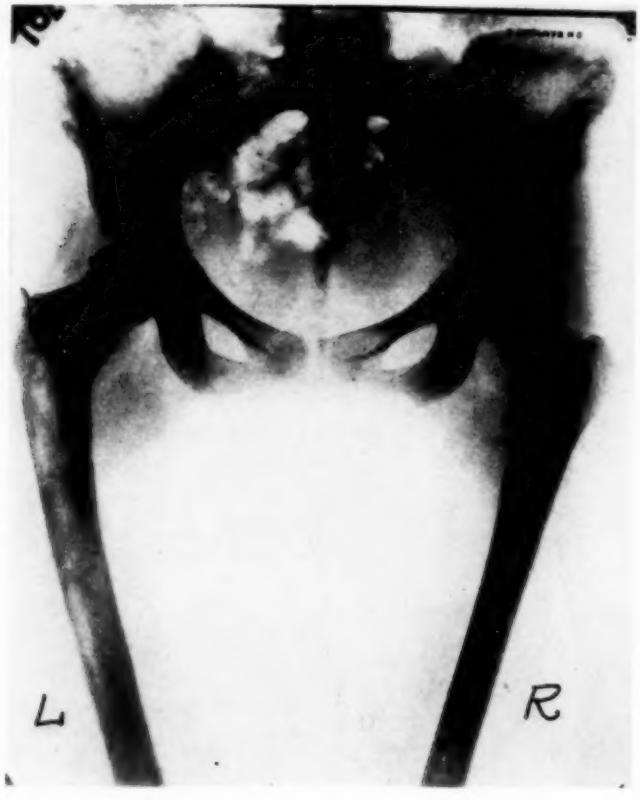

FIG. 7. Showing areas of bone absorption in left ilium, left pubic bone and left femur. The neck of the left femur is thick and coarse; the inferior surface appears to be splintered.

not show early maturation of the skeleton as do the females, even though the roentgen lesions of the bones have the same gross appearance.

In the syndrome under discussion surgical explorations for parathyroid, ovarian and adrenal lesions have been negative. Autopsies have been few and incomplete, but a very exhaustive one, that by Sternberg and Joseph [16] on the case reported earlier by McCune and Bruch, failed likewise to supply an anatomic basis for the clinical picture. Since structural changes which might elucidate the clinical picture have not been demonstrated in any of these cases, we must turn to physiologic mechanisms for an explanation of the profound changes noted.

In considering these physiologic mechanisms attention must be directed to the

fact that although endocrine syndromes may be definitely patterned, e.g., Graves' disease, Simmonds' disease, etc., many will show curious admixtures of features of various types depending on the particular variable which may be involved.

Until definite experimental or clinical proof or both is available for all conditions, the explanation of many clinical pictures will remain in doubt. However, recent developments in neuroendocrine physiology offer tempting paths for exploration and the author feels that in the syndrome under discussion some contribution to the analysis of the clinical condition can be made.

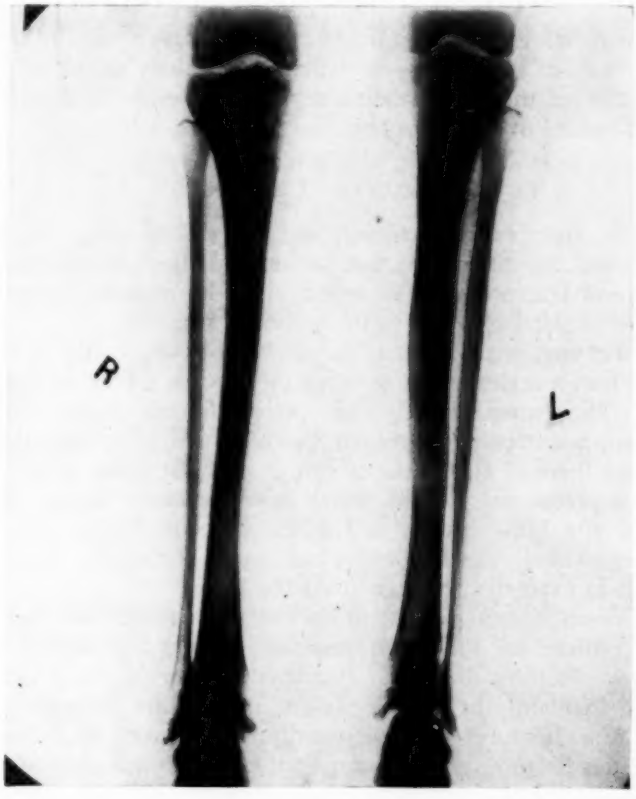

FIG. 8. Showing areas of bone absorption in left tibia. The epiphyses are closed.

PRECOCIOUS PUBERTY

That a central mechanism, rather than a peripheral one, may be responsible for precocious sexual development is granted by many authors, e.g., Novak,[17] Weinberger and Grant,[18] Sternberg and Joseph,[16] and Bing, Globus and Simon.[19] In fact, Novak, in commenting on the syndrome under discussion, suggests that the precocious puberty of this group is of the "cerebral type." The other authors just mentioned consider the hypothalamus the particular area responsible.

It is generally accepted now that the "anterior lobe of the pituitary is the master gland of the endocrine system." [22] The hypophysis itself is controlled by nervous

as well as other glandular factors. Normally something occurs about the time of puberty which releases the pituitary from its inhibiting factors, and the activity of the gland is now seen in the remarkable growth of the body and the development of sex characteristics. In the opinions of Weinberger and Grant [18] and Bing et al.[19] the factor of release resides in the hypothalamus. Smith and Dortzbach [20] have demonstrated the presence in the pituitary gland of gonad stimulating hormones even in the fetus. From these facts it may be reasonably deduced that a premature release of the restraining influence over the hypophysis could result in precocious puberty. What initiates the early release of these hormones cannot always be precisely indicated, but cranial injuries, intracranial tumors and encephalitis have been noted as precursors in cases of this type.[18,19,21]

In the author's case it is suggested that some injury might have occurred at birth which affected the hypothalamic region sufficiently to disturb the normal hypothalamic control over the hypophysis.

Skeletal Changes

The skeletal changes are striking, and indeed, in many cases, have completely dominated the clinical picture because of their distribution and results (deformities and fractures). The question to be answered next is the relationship of the skeletal changes to the pubertas praecox.

Bremer [23] has suggested a plausible mechanism which fits in well with our concepts. "From a series of experiments on rats the following possibilities may be inferred: The general disease (i.e., osteitis fibrosa cystica) may be caused by a long continued excess of estrogen, probably acting through the parathyroid glands." That there is an excess of estrogen in the cases under discussion is evident by the precocious puberty which is so important a feature of this syndrome. That the bone lesions are specifically due to parathyroid activity seems to be most likely in view of the fact that it is the only known physiologic process which can mobilize calcium from the bones.

However, even if one were to insist on further evidence before accepting the foregoing, there are numerous instances of the association of hyperparathyroidism and pituitary diseases. Parathyroid tumors and bone disease have been reported frequently in acromegaly and in pituitary basophilism.

That the other features of hyperparathyroidism, such as hypercalcemia and negative calcium balance are not seen in these cases merely indicates that the process has been a slow one and the daily changes in blood chemistry so small that detection is not easy. It has been estimated quantitatively [15] that the normal skeleton contains about 900 grams of calcium; 3 to 6 grams could be lost per month without evidence either in blood chemistry or roentgenograms. However, after a long time, the latter might show osteoporosis or bone cysts—the results of calcium loss—without any detectable changes in blood chemistry. Also, when bone cysts or osteoporosis are present the process may have stopped and all that is visible is the end result.

Objection has been raised to the hormonal explanation of the bone disease on the ground that the lesions are frequently unilateral and not diffuse. This objection can be countered by many instances of asymmetrical or unilateral lesions in endocrine disease. Sternberg and Joseph [16] cite numerous examples such as unilateral exophthalmos in exophthalmic goiter, unilateral acromegaly

(also reported by Lichtwitz [15]), unilateral hemihypertrophy and hemiobesity; unilateral gynecomastia with cortical adrenal and testicular tumors; patchy and asymmetric changes in the bones in renal rickets have been described. It is recognized that the action of a hormone depends not only on its presence but also on local tissue susceptibility to the action of the hormone. Perhaps in the cases under discussion there is some underlying neurologic lesion which determines the variation in tissue response.

Pigmentation

Little is known of the mechanism which produces this feature and the author leaves the elucidation of this symptom to future investigations.

Conclusion

An additional case is presented, exhibiting the triad of symptoms:

1. Precocious puberty.
2. Fibrocystic bone changes.
3. Pigmentation of the skin.

The pathologic physiology is discussed and the hypothesis is advanced that the syndrome results from a hypothalamic (pituitary) parathyroid disturbance.

Acknowledgments

The author wishes to express his gratitude to Drs. George Baehr and Paul Klemperer of Mt. Sinai Hospital, New York, for permission to use the data from the Consultation Service and the Department of Pathology.

The late Dr. Leopold Lichtwitz made many valuable suggestions in the interpretation of the clinical picture of the patient herein reported.

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INFECTIOUS MONONUCLEOSIS: A CASE FOLLOWING A SKIN ABRASION ON THE RIGHT LEG, AND INVOLVING ONLY THE RIGHT INGUINAL LYMPH NODES *

By Norman Larue Anderson, M.D., *Black Mountain, N. C.*, and Robert Humber Cox, M.D., *Lynchburg, Va.*

The following case report is presented not only because it is, we believe, the first reported case of infectious mononucleosis following a known skin lesion, but also because it may offer additional evidence concerning the nature of the disease.

Case Report

The patient was a 27 year old white male physician living in a rural community. On September 14, 1942, he noted a small, slightly tender indurated area on the skin covering the lower internal aspect of the right tibia. This area was surrounded by an

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ecchymotic zone measuring about 4 cm. in diameter. The patient did not remember the cause of this lesion and considered it to be an insect bite at first.

On September 17 the patient became aware of moderate enlargement of the right inguinal lymph nodes where considerable tenderness also was apparent. On September 19 he began having a daily fever ranging from 99.6 to 101° F. The pulse rate averaged around 90 beats a minute. One of the right inguinal nodes enlarged to about 2 cm. in length and 1 cm. in width, the tenderness having increased. The patient went to bed on September 20, 1942, suffering from general malaise, weakness, neuralgic aches in most of the joints, a severe right parietal headache, and a mild erythematous macular rash over the back and buttocks which occurred on the fourteenth day after the onset. The fever and soreness of the right inguinal lymph nodes persisted for about 25 days. No other lymph nodes except the right inguinal ones were ever involved during the course of the disease, and the spleen was never palpable or tender. Both cold and hot compresses applied to the area gave questionable relief from discomfort.

Consecutive blood counts and smears done from the onset of fever exhibited a typical picture of infectious mononucleosis with the mononuclear cells reaching a maximum of 73 per cent of the total leukocytes on October 8. Leukopenia was characteristic at the onset with a total of 3,300 leukocytes on September 23. The sedimentation rate (Cutler), normally 2 mm. in one hour for the patient, was 5 mm. in one hour on September 23, and 3 mm. in one hour on October 5. Urine and stool analyses were negative. The patient made a prolonged but uneventful recovery, feeling normal again in six weeks' time. The primary lesion on the leg healed and the right inguinal lymph nodes regressed to normal size. The blood picture also returned to normal as evidenced by a blood count on October 30 (see table for consecutive blood counts).

TABLE I*

Date	Time	Hgb.	RBC.	WBC.	PMN.	Juv.	Lymph.	Mono.	Eos.
3–26		90%	4.3	6,100	69%		28%	2%	1%
†9–23	10 a.m.	90%	4.3	3,300	50%		46%	4%	
9–25	10 a.m.			4,500	28%	(7%)	48%	21%	3%
9–27	4 p.m.			8,400	25%	(2%)	65%	8%	2%
9–29	4 p.m.			9,200	25%	(3%)	69%	4%	2%
10–1	4 p.m.			8,200	38%		58%	4%	
10–3	10 a.m.			9,400	34%	(2%)	57%	8%	1%
10–5	10 a.m.			7,600	31%		64%	4%	1%
10–8	11 a.m.			7,400	26%		71%	2%	1%
10–13	11 a.m.	82%	4.1	5,200	30%		64%	5%	1%
10–17	11 a.m.			4,700	40%		54%	5%	1%
10–22	11 a.m.			5,200	46%		46%	8%	
10–24	5 p.m.	90%	4.9	7,600					
10–30	4 p.m.			6,400	56%		32%	8%	4%

* Compilation of the blood counts was made with the technical assistance of Miss Corneil Varner.

† Onset of infectious mononucleosis.

Heterophile antibody agglutinations with sheep cells done on blood serum at the Piedmont Hospital in Atlanta according to the method of Paul and Bunnell [1] were positive. On October 2 there was positive agglutination at 1:128 dilution, and on October 8 the positive titer had decreased to 1:64. Since the serum specimens were mailed unrefrigerated a distance of 70 miles before testing, it is possible that the antibody titers were considerably higher at the bedside. According to Kracke and Garver [2] a positive agglutination in a dilution of 1:64 is considered diagnostic in the absence of serum sickness, whereas Straus and Bernstein [3] consider a dilution

of 1:512 as diagnostic, although they occasionally make the diagnosis of infectious mononucleosis in cases not showing a positive agglutination at any titer. There was no history of serum sickness in the patient, and the same test, done 18 months previously, had been negative. As indicated by Straus and Bernstein, a falling titer at weekly intervals is much more significant than single determinations.

Representative blood smears were sent to Dr. Roy R. Kracke of the Department of Pathology at Emory University and he reported as follows: "The smears show a predominance of lymphocytic cells exhibiting a considerable variation in morphology: some being large, others small, some showing vacuolated cytoplasm, others showing dark, intensely stained blue cytoplasm: a few have the appearance of monocytes. This pleomorphic picture, including these various cell types, is quite characteristic of infectious mononucleosis, and I feel quite certain that this is the disease involved, particularly considering the lymphadenopathy. I would expect the heterophile antibody test to be positive."

Discussion

The etiology of infectious mononucleosis has yet to be established definitely. In 1929 Nyfeldt [4] produced the typical blood picture of infectious mononucleosis in rabbits by exposing them to *Bacterium monocytogenes*. Later, in 1929, Gorham, Smith and Hunt [5] also produced the typical blood picture in guinea pigs by inoculating them with the membrane from the pharynx of a young girl who had Vincent's angina.

Later evidence, however, indicates that the etiological agent is a virus. Nettleship [6] in 1942 succeeded in producing an ectodermal proliferation and monocytic cell infiltration in the chorio-allantoic membrance of chick embryos by inoculating the embryos with sterile Berkefeld filtrates of nasal washings and blood obtained from cases of human infectious mononucleosis. No inclusion bodies were found, but a suspension of similarly treated ground chick membranes when injected into rabbits caused a monocytosis, but failed to produce a significant heterophile antibody response.

Recently Bornstein [7] demonstrated, in an interesting case of severe cystitis, a positive heterophile antibody reaction of the serum. A strain of *Escherichia coli* was cultured from the blood of this case, and this culture contained heterophile antigen. The antibodies could be differentiated from those observed in serum sickness and in infectious mononucleosis, and were of Forssman's type.

In the case reported it seems possible that the infecting agent, instead of taking the usually considered route through the upper respiratory system and causing pharyngitis with regional lymph node involvement, was probably introduced through an abrasion on the right leg causing a regional involvement of the right inguinal nodes only, but producing the typical systemic symptoms and blood picture of infectious mononucleosis, along with positive heterophile agglutination tests. Since the patient regarded his initial lesion as an insect bite, could this mean that perhaps infectious mononucleosis might be transmitted through an insect vector as well as through the usually considered respiratory route?

Summary and Conclusions

1. A typical case of infectious mononucleosis following a skin abrasion on the right leg, and involving the lymph nodes only of the right inguinal region is presented. This is believed to be the first case of this nature reported.

2. It is thus evident that the infecting agent of infectious mononucleosis, whether it be bacterial, virus, or otherwise, may possibly gain access to the body by other than the almost exclusively reported respiratory route.

3. It is interesting to note that, as in other local infectious processes, infectious mononucleosis is primarily a local process, causing predominant symptoms in the local lymph nodes draining the infected area, and causing the typical systemic symptoms regardless of the site of entry.

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A CASE OF TETRALOGY OF FALLOT WITH VERRUCOSE ENDOCARDITIS *

By Lawrence Perlman, M.D., and Jacob Meyer, M.D.,
Chicago, Illinois

A majority of the cases of the cyanotic group of congenital cardiac anomalies present the combination known as the Tetralogy of Fallot.

Most of these cases are encountered in infants and children, the mean age in Abbott's [1] series being 12 years of age. White and Sprague [2] reported a case of Tetralogy of Fallot in which the patient lived to the age of 59 years and nine months. This is the oldest proved case on record. Fallot,[3] in his original article, reported a case which lived to 36 years of age. Revilloid [4] also reported a case of the Tetralogy in a 36 year old female. LaFitte's patient [5] died at the same age.

More recently, Volini and Flaxman [6] reported the Tetralogy in a male who lived to 41 years of age. In 1939, Herndon, Voss and Donovan [7] reported a case which lived to the age of 49 years.

The case we are reporting is the seventh oldest proved case of the Tetralogy of Fallot on record. Of particular interest is the heavy manual labor which the patient performed during his lifetime, despite the presence of a lesion which is supposedly incompatible with longevity or a useful physical activity.

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From the Department of Medicine, Cook County Hospital.

It is generally supposed that death is caused by the development of bacterial endocarditis or else by pulmonary tuberculosis, and it was of the former condition that our patient died. However, in Abbott's series [1] of 51 cases, which is the largest reported, only one patient had a superimposed bacterial endocarditis. Fallot's [3] case also died of a terminal endocarditis. Pescatore, Wolffe, and Digilio [8] reported a case of Tetralogy of Fallot in a 20 year old male who died of a septic endocarditis. The remainder of the cases of Tetralogy of Fallot which have been reported died of causes not related to the cardiac defect. Therefore, it would seem that the occurrence of a bacterial endocarditis, on such a congenital cardiac defect as the Tetralogy of Fallot, is not so frequent a finding as we have been led to believe.

Case Report

W. H., a 32 year old, white male, was first admitted to the Cook County Hospital on January 9, 1941, with complaints of dyspnea, chills and fever of nine days' duration and precordial pain of four days' duration. He had a congenital cardiac lesion, having been cyanotic since birth. There was no history of any previous

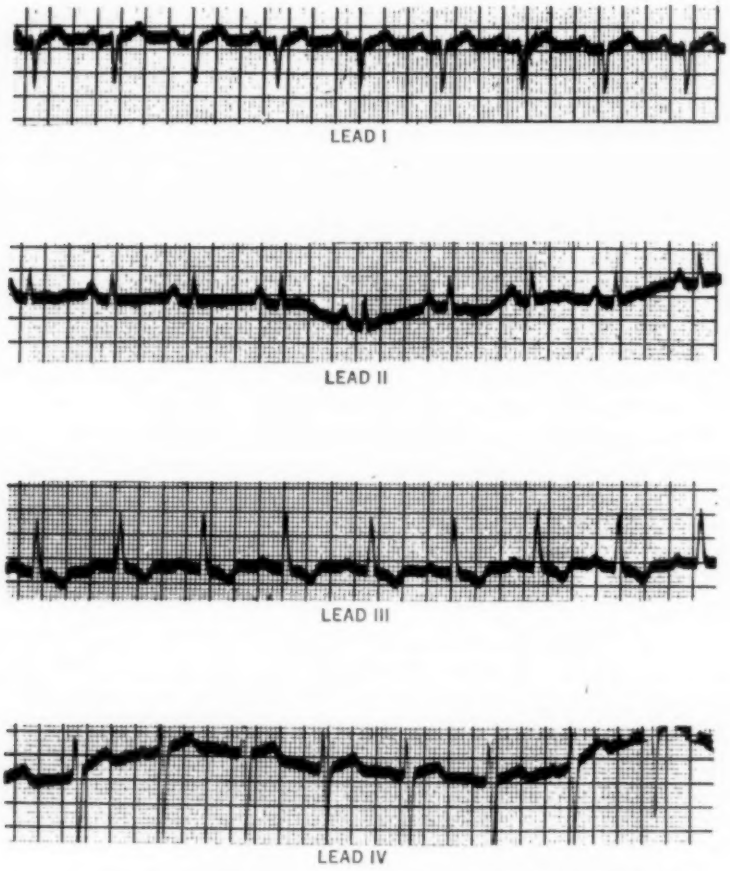

Fig. 1. Electrocardiogram showing marked right axis deviation.

attacks of cardiac decompensation, and the patient had been working as a truck driver up to the onset of his present illness. He had previously been dyspneic on strenuous exertion, but never sufficiently so to warrant his going to bed.

He had had scarlet fever at the age of 10 years, and an appendectomy at the age of 17 years. No history of rheumatic fever was obtained, although during childhood he suffered from frequent sore throats.

Physical examination at the time of admission revealed a well developed, well nourished, young male who was in moderate respiratory distress and was deeply cyanotic. His temperature was 98° F., his pulse 84 per minute, and respirations 24 per minute. The blood pressure was 92 mm. Hg systolic and 68 mm. diastolic. The

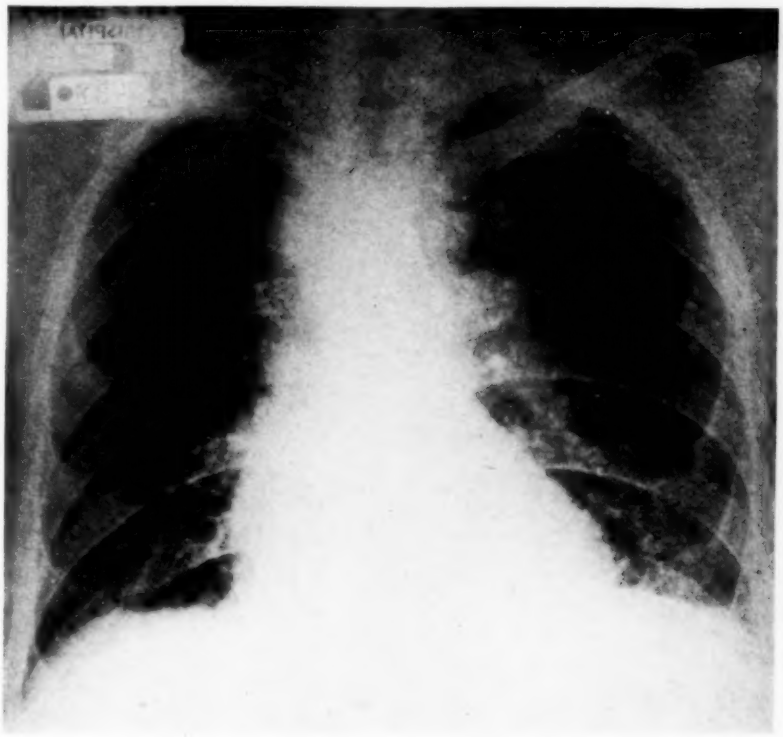

FIG. 2. Postero-anterior view of chest showing evidence of right upper mediastinal widening and enlargement of right heart border.

chest showed dullness to percussion at both bases with an absence of breath sounds and decreased tactile fremitus at the left base. The cardiac borders were five centimeters to the left of the sternum in the fifth interspace and one and one half centimeters to the right of the sternum. The cardiac rhythm was regular. Auscultation revealed a systolic murmur at the apex and also at the base. This murmur increased in intensity, to reach a maximum in the third left interspace where it was heard as a rumbling and blowing sound. The liver was palpable two centimeters below the right costal margin. No other abdominal masses were palpable. There was marked clubbing of the fingers and toes with an intense cyanosis of the nail bed. There was no peripheral edema.

The patient was placed on three grains of digitalis a day for one week, while

at complete bed rest. After this interval, as his dyspnea progressively diminished, he was allowed up. He was discharged nine days after admission.

He was seen in the Cardiac Clinic as an outpatient on January 28, 1941. Since his discharge from the hospital he had been taking a grain and a half of digitalis every day and limiting his activity. His condition was good, there being no evidence of cardiac decompensation.

Nothing further was heard from him until May 5, 1941, when he was readmitted to the hospital with complaints of pains in both feet and in his right arm and hand of one week's duration. On admission his temperature was 100.4° F., pulse rate 92

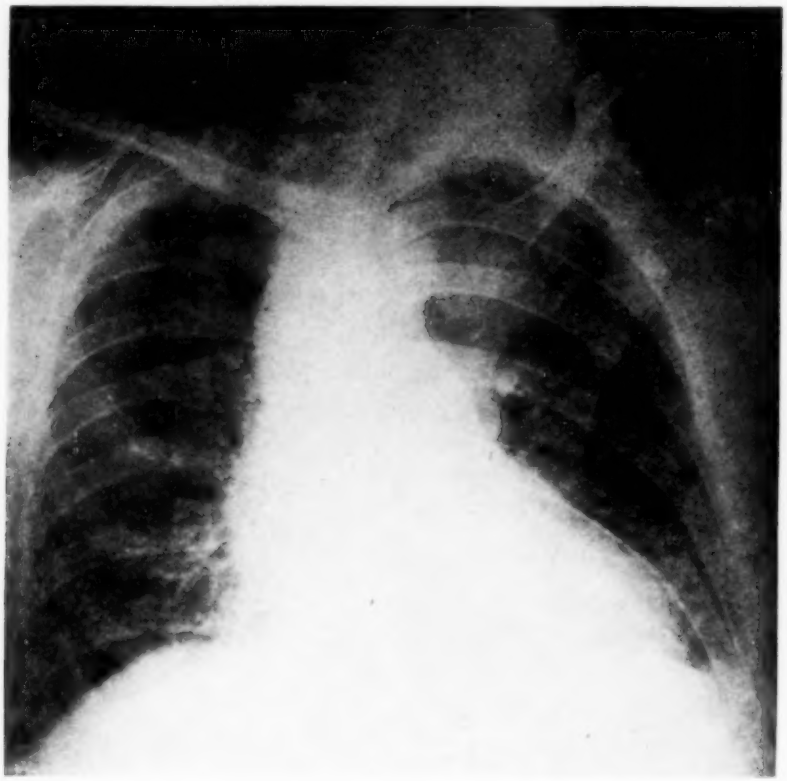

FIG. 3. Left oblique view of chest showing aortic knob on right side.

per minute, and respiratory rate 28 per minute. Examination of the chest and heart revealed findings essentially similar to those on the first admission. Of significance were the presence of petechiae in the conjunctiva of the right eye, extreme pain on pressure over the toes and the fingers of the right hand, and a firm, blue, elevated lesion one centimeter in diameter on the left palm. The spleen was not palpable.

The temperature, during his entire hospitalization, was elevated between 99.6° and 102° F., reaching 106° F. before death. Repeated blood cultures during this time were consistently negative. One week after admission the palmar lesion became fluctuant and was aspirated. A few drops of thick whitish blood-tinged fluid were obtained, direct smear of which showed an occasional chain of faintly staining cocci. Culture of the fluid showed small, gram positive cocci in pairs and in short chains.

Five grams of sodium sulfathiazole were given intravenously on May 13 and repeated on May 14. For two days thereafter sulfathiazole (2 gm. every 4 hours) was given orally. At the end of this time a diffuse erythematous rash was noted, along with nausea and vomiting, and the drug was stopped. On May 21, sulfanilamide (1 gm. every four hours) was started and continued to May 30. During the entire course of sulfanilamide therapy the temperature was not affected. He died on May 31, 1941, 26 days after his second admission.

Laboratory Data: Daily urine examinations at the time of his second admission consistently showed red blood cells, white blood cells, and granular casts. There was a slight elevation of the non-protein nitrogen, the values being as high as 54 mg. per 100 c.c. The blood Wassermann reaction was negative. There was a gradual

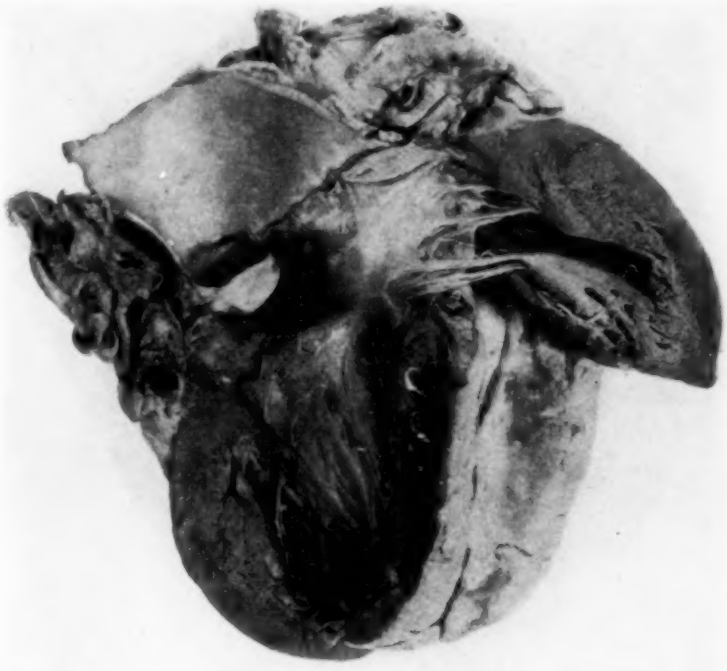

FIG. 4. Left ventricle showing interventricular septal defect with aorta riding both right and left ventricle.

diminution in the hemoglobin and red blood cell count, from 132 per cent hemoglobin and 6.72 million red blood cells at the time of his first admission to 98 per cent hemoglobin and 5.0 million red blood cells, six days before patient died. During this time the white blood cell count rose from 8,300 cells per cubic millimeter to 24,600 cells per cubic millimeter shortly before death.

Electrocardiograms showed a marked right axis deviation (figure 1).

Roentgenographic examination of the chest revealed a fullness of the right upper mediastinal shadow (figure 2). The aortic knob could not be made out. On fluoroscopy the right mediastinal widening was seen to be due to the aortic arch and was well shown by a left oblique view (figure 3).

A clinical diagnosis of Tetralogy of Fallot with superimposed bacterial endocarditis was made.

Permission for necropsy limited to the heart only was obtained.

Autopsy (performed by Dr. William Shaeffer). The pericardial sac contained 60 c.c. of a clear yellow fluid. The heart weighed 425 grams. The myocardium was dark purple red and firm. The left ventricle measured 15 millimeters in thickness and the right ventricle was 11 millimeters in thickness.

The pulmonary artery was markedly stenosed, the mouth measuring 32 millimeters in circumference. There were two large valves, one having a small septum partially

FIG. 5. Right ventricle showing relative thickness of wall, mural thrombus located on tricuspid valve.

dividing this leaf. There was a slight fusion of the leaflets at the commissures. Just below the pulmonary valve there were small bead-like projections, one millimeter in diameter, on the endocardium. The intima of the pulmonary artery was smooth and shining.

The right auricle and the right ventricle were markedly dilated. The transverse diameter of the right ventricle was 16 centimeters and the vertical diameter was the same. The tricuspid valve showed thickening of the free edge by atheromatous plaques. On one of the leaflets of the tricuspid valve was a large, friable, purple red vegetation which measured 2.5 by 2 by 1.5 centimeters.

The free edge of the mitral valve was thickened by atheromatous plaques. The chordae tendineae were thickened and fused.

The aorta measured 78 millimeters in circumference and its intima contained single fatty and hyaline plaques. Just below the aortic valve there was a defect in the interventricular septum which measured 2.5 centimeters in diameter. The right leaflet of the aortic valve was continuous with the endocardium of the right ventricle.

The left coronary artery was thin walled with a smooth intima. The right coronary artery had a double ostium. The wall was slightly thickened, the lumen was dilated, and the intima contained fatty and hyaline plaques.

The anatomic diagnosis was:

1. Congenital cardiac deformity, with
   a. Interventricular septal defect
   b. Stenosis of the pulmonary artery
   c. Marked hypertrophy and dilatation of the right ventricle
   d. Bicuspid pulmonary valve
   e. Dextrorotation of the aorta
2. Verrucose vegetations of the tricuspid valve.
3. Double ostium of the right coronary artery.
4. Endocardial sclerosis.
5. Slight fibroplastic deformity of the mitral valve.

Discussion

The criteria for the diagnosis of the Tetralogy of Fallot are essentially similar to those originally promulgated by Fallot [3] in 1888 and added to by McGinn and White in 1936. The diagnostic points include:

1. Cyanosis which has been present since birth.
2. Marked pulmonary osteoarthropathy.
3. Polycythemia.
4. The presence of a loud systolic murmur heard best at the pulmonic area.

In the presence of these four clinical findings, the Tetralogy of Fallot may be suspected.

Confirmatory evidence may be obtained by roentgenogram. The widening of the right upper mediastinum and the absence of an aortic knob on the left (figures 2 and 3) are very suggestive of dextroposition of the aorta. On fluoroscopy, the right upper mediastinal widening may be identified as the pulsating aorta. The electrocardiogram shows a marked right axis deviation (figure 1).

Since the case which we presented conformed to most of these criteria, a clinical diagnosis of Tetralogy of Fallot was made. The febrile course, the presence of petechiae and the palmar lesion suggested the presence of a superimposed endocarditis. This diagnosis was made despite the consistently negative blood cultures. The postmortem findings confirmed the clinical impression.

Summary

A case of Tetralogy of Fallot in a 32 year male who died of a bacterial endocarditis is presented. The diagnosis was made clinically and verified by post mortem examination. The salient features in the diagnosis of Tetralogy of Fallot are presented.

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ANOTHER CASE OF INTESTINAL MYIASIS *

By Marcus W. Lyon, Jr., M.D., and John D. Mizelle, Ph.D.,†
Notre Dame, Indiana

Whereas larvae of *Gastrophilus* species which produce horse bots are true intestinal parasites, larvae of other genera (*Lucilia, Calliphora, Piophila, Fannia, Phormia, Musca,* etc.) are apparently plastic enough in their habits to live for different periods of time in the digestive tract of mammals.

The older opinion regarding the prevalence of intestinal myiasis is well expressed by Walsh who says, "Taking everything into consideration, we doubt whether, out of ten thousand cases, where the larvae of two-winged flies have existed in considerable numbers in the human intestines, more than one single case has been reported in print by competent entomological authority for the edification of the world" (Banks 1912). The accumulated data available at present indicate that many ingested fly larvae do not survive the environmental conditions of the digestive tract whereas others do. The latter produce intestinal myiasis of different degrees of intensity.

Precisely how fly larvae acquire entrance to the digestive tract is not clear. Entrance is generally thought to occur by way of the mouth but it seems entirely possible and very probable that entrance may also be secured by way of the anus. Herms and Gilbert (1933) say that it is easy to understand how larvae of the cheese fly (*Piophila casci*) might be ingested since they normally occur in foods such as cheese, bacon, ham, etc., but that this view is not plausibly tenable with reference to commonly reported infestations by larvae of the lesser house fly (*Fannia canicularis*) and the latrine fly (*F. scalaris*), whose food is principally fecal material. These authors point out that these species under

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† Dr. Marcus W. Lyon, Jr., formerly of the South Bend Clinic, South Bend, Indiana died May 18, 1942. The junior author is a member of the Department of Biology, University of Notre Dame, Notre Dame, Indiana.

stress of circumstances may be compelled to lay their eggs in decomposing vegetable matter or meat. Neveu-Lemaire (1912) says that *Lucilia sericata* often lays its eggs on the thin skin of the rumps of sheep and after hatching, the larva penetrate and live in the tissues of the animal. Chandler (1941) reported a case of urinary myiasis caused by a species of *Lucilia,* probably *L. sericata.* Entrance in this case probably occurred by way of the vaginal orifice. Riley and Johannsen (1938), however, suggested that larvae of *Psychoda albipennis* migrated from the rectum into the bladder of a child exhibiting urinary myiasis. The present case involves larvae of *L. sericata* and an undetermined species of *Sarcophaga.*

Case Report

A 23 year old housewife (Mrs. W. B.) living in an unscreened house in the residential part of South Bend, Indiana, consulted the South Bend Clinic on several occasions for various complaints. In 1938 she complained of a burning sensation on urination. At that time her appetite was good and her bowels were regular without the use of laxatives, but she occasionally became nauseated and vomited after eating. In July 1940 her urinary condition became worse and necessitated her getting up at night. Her doctor at that time said she had bladder trouble. Physiological conditions present immediately prior to the onset of menstruation seemed to intensify the symptoms and her menstrual periods, otherwise normal, became painful especially during the first two or three days. Nausea and vomiting became frequent. Wassermann, Kline, Mazzini, and pregnancy tests were negative; erythrocytes numbered 4,030,000 (with slight hypochromia), hemoglobin 10.44 gm. per 100 c.c., leukocytes 6,000 with an essentially normal differential count. In December 1940, she consulted the clinic again, complaining of abdominal distress. Examination revealed a possible cyst of the right ovary. A hemorrhagic cyst about the size of a hen's egg was removed. Recovery was uneventful and two months later she reported that her bladder condition was better.

On July 5, 1941, the patient said that she thought she saw worms in her stools and submitted one (stool) for examination. It was of normal color and consistency and negative except for a few threads (10–12 mm. long) of definite plant origin. On August 5, 1941 she submitted another stool of the same general nature except that it contained many large dipterous larvae (about 10 mm. by 1½ mm. in diameter). When the patient first reported the "worms" she had the opinion of her physician that they were ordinary pin worms and gentian violet had been prescribed and taken without effect. This was one month before she submitted the stool containing the vegetable fibers. The patient was of the opinion that she passed "worms" in her stools for a period of one month.

For the sake of completeness the following additional information is given: Weight 113 pounds (lost 9 lbs. in summer of 1940), rather thin and poorly nourished, pulse 124 and of good volume, blood pressure 130 mm. Hg systolic and 60 mm. diastolic, sedimentation rate normal, temperature normal, tongue and tonsils normal, sinuses normal, thyroid normal, lungs clear, a harsh systolic murmur present over apical region, liver and spleen impalpable, appendectomy (1930) scar well healed, patellar reflex active, pupils equal and regular, several teeth missing, one tooth carious. No children. Mother and father living and well, has two brothers and a sister. Uses neither alcohol nor tobacco. She complained of "heart trouble" since 1932. At the time of the intensification of her urinary condition (July 1940) she was teaching school and drove 65 miles daily. Her urine at the time was normal except for a high specific gravity (1.026) and a pH of 7.5.

The present case, characterized by the symptoms of nausea, vomiting, and abdominal distress was conspicuous by the absence of diarrhea which is generally one of the chief symptoms of intestinal myiasis. The history regarding the urinary trouble is interesting since Chandler (1941) recorded a case of urinary myiasis with essentially the same symptoms, which suggests that the present case possibly manifested urinary complications. How the larvae entered the intestinal tract is not known. Extracorporeal contamination of the feces seems remote and was ruled out entirely in the case reported by Herms and Gilbert (1933).

Most interesting perhaps is the tenacity of infestations of this sort. Although apparently of superior intelligence, this woman lived in an unscreened house and complained of a large number of flies. It is most unusual that an individual of this apparent type could knowingly or accidentally ingest large fly larvae sufficiently often to account for an infestation of a month's duration. The larvae were large enough to be readily noticeable as well as repugnant to a normal individual. If they were ingested when small enough to escape detection, it naturally follows that they developed considerably in the human digestive tract which, to say the least, seems very remarkable. This possibility however, is not untenable since Parker (1922) is of the opinion that *Calliphora erythrocephala* is not only capable of living in the digestive tract of man but actually reproducing in it paedogenetically. Herms and Gilbert (1933) state that the chances of reinfestation were supposedly nil during one year in an obstinate case of intestinal myiasis which was apparently of several years' standing.

The larvae in the present case were preserved when received by the senior author but were reported alive when passed by the patient. Living larvae of the cheese fly (*Piophila casei*) were recovered from a bloody human (child) stool in 1901 by Thebault, according to Riley and Johannsen (1938) and experimentally from a dog by Herms and Gilbert (1933). The last-named authors (1933) recovered living larvae of the genera *Calliphora, Sarcophaga,* and *Lucilia* from a human case of intestinal myiasis. Intestinal myiasis has also been reported for the larvae of *Fannia scalaris, F. canicularis, Musca crassirostris, Apiochaeta rufipes, Musca domestica, Eristalis tenax, Sarcophaga hemorroidalis, Hermetia illucens,* etc. (Chandler 1940, Riley and Johannsen 1938).

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EDITORIAL

TREATMENT OF SUBACUTE BACTERIAL ENDOCARDITIS

SUBACUTE bacterial endocarditis has long aroused the keen interest of physicians, an interest which is perhaps a little out of proportion to the frequency of its occurrence as compared with many other infections. This is doubtless due in part to the highly variable and often bizarre clinical symptoms which it presents, although certain of these are so characteristic that the diagnosis should be suspected if not positively made in a large majority of the cases if the observer is alert to the possibility of its occurrence. Interest is also stimulated by the course of the disease which, in spite of its frequently apparent mildness, relatively slow course and occasional remissions, proceeds inexorably to a fatal termination in most cases in spite of any type of treatment which hitherto has been available. The fact that arrest or apparent recovery occurs in rare instances (about 1 per cent of the cases) has served largely to tantalize those interested in other victims of the disease and to arouse false hopes as to the efficacy of some therapeutic procedure which happened to be under trial at the time.

The introduction of the sulfonamides and more recently of penicillin naturally led to a trial of these drugs in subacute bacterial endocarditis. Although the results thus far reported have been disappointing, they are, nevertheless, somewhat more favorable than those obtained by older methods of treatment. Among others, Kelson, White and their associates have made a particularly careful study of this problem, and we are fortunate in being able to present in this number of the Annals of Internal Medicine reports of their most recent investigations.

As these investigators clearly point out, the problems involved in the treatment of subacute bacterial endocarditis differ notably from those encountered in the case of most other infections. Although this disease may be caused by several different species of bacteria, in a large majority (about 95 per cent) of the cases some nonhemolyzing type of streptococcus is involved. These streptococci usually have little or no virulence for laboratory animals. In man they normally lead a saprophytic existence in the mouth and throat, they show little or no tendency to invade the tissues, and although they frequently enter the blood stream in small numbers, they are quickly eliminated by the normal defensive forces unless they find unusual conditions especially favorable for their development.

As is widely known, these conditions are found largely in heart valves (or mural endocardium) which have been injured, usually by rheumatic fever, or which are congenitally defective. In the thrombi which form in such areas, the streptococci find conditions favorable for their development, in that they have abundant nourishment and are protected mechanically from phagocytosis and probably to some extent, at least, from the anti-

bodies (and possibly from antibacterial drugs) which are usually abundant in the plasma. It appears to be the inaccessibility of the organisms rather than any inherent virulence on their part which makes possible their continued development and thus brings about the progressive course and unfavorable outcome of the infection. Indeed, endocarditis in the only human disease which has been proved to be caused by these organisms.

Kelson and White have analyzed the factors which appear to restrict the effective action of the sulfonamides in this disease. They stress particularly the readiness with which the streptococci acquire resistance to the sulfonamides, although the organisms as a rule are initially sensitive to these drugs. Resistance is especially apt to develop if a previous course of sulfonamide has been given which was inadequate either in dosage or duration, or if treatment is interrupted because of drug intoxication and resumption is attempted later. Resistance appears sooner or later, however, during the first uninterrupted course of treatment, and these observers have found that organisms which have acquired resistance to sulfapyridine, the most potent sulfonamide in this infection, are resistant to the others also.

They also point out that the sulfonamides exert a bacteriostatic rather than bactericidal action on the organisms, and elimination of the latter depends upon the natural defensive forces of the body, particularly phagocytosis. The action of the latter is largely blocked by the location of the organisms within the thrombi.

To offer a reasonable hope of being effective, therefore, treatment must first make the organisms accessible to attack; and second, the drug must be given early, in adequate dose, and without interruption because of symptoms of drug intoxication, unless the latter are so severe as to be an immediate and grave risk to life. The first requisite they attempt to secure by the administration of heparin in dose sufficient to slow coagulation and thus presumably to limit the development and enlargement of the thrombi while the antibacterial agent is being administered. In addition to two cases previously published,[1] the authors report 10 additional recoveries in a series of 34 cases treated by this method. These results, although they still leave much to be desired, are substantially better than those which have been obtained with sulfonamides alone.

Other observers have not obtained such favorable results with these measures.[2] Katz and Elek,[3] for example, even feel that the use of heparin should be abandoned. As Kelson has pointed out, however, in many of these unsuccessful cases the treatment was not properly administered. There is rarely any observation as to the susceptibility of the strain of streptococcus to the drug. In many cases sulfonamides have been given in interrupted

[1] KELSON, S. R., and WHITE, P. D.: A new method of treatment of subacute bacterial endocarditis, Jr. Am. Med. Assoc., 1939, cxiii, 1700.

[2] LICHTMAN, S. S.: Treatment of subacute bacterial endocarditis: current results, Ann. Int. Med., 1943, xix, 787–794.

[3] KATZ, L. N., and ELEK, S. R.: Combined heparin and chemotherapy in subacute bacterial endocarditis, Jr. Am. Med. Assoc., 1944, cxxiv, 149–152.

courses, a procedure which frequently results in the development of drug fastness. Frequently, too, heparin was not administered simultaneously with the sulfonamide. There is general agreement that heparin alone is ineffective. Serious objections have been advanced to the use of heparin because of the danger of inducing hemorrhage, particularly cerebral hemorrhage. A substantial number of such accidents have been reported.[3] Kelson himself reports this complication in three of 40 cases during treatment, but he claims that deaths due to cerebral accidents were not more frequent in patients so treated than they had been before the use of heparin was inaugurated. The data now available are not sufficient to establish how great this risk really is. However, if further experience shows that a recovery rate of 30 per cent or better can be maintained, one would be justified in incurring a substantial risk of bleeding in a disease in which the outlook otherwise is so nearly hopeless.

There is good reason, also, to believe that the details of treatment can be improved. It may prove possible to simplify the technic by substituting dicoumarin orally administered for heparin by vein, although at present the activity of the former cannot be so precisely controlled. It is more likely that penicillin may supplement or replace the sulfonamides as an antibacterial agent. Penicillin is far less toxic than the sulfonamides, and it appears that the organisms are much less prone to become resistant to its effects. Although the permanent results thus far reported from the use of penicillin alone are not substantially better than those obtained with the sulfonamides,[4] Loewe et al.[5] have reported immediate favorable results with sterilization of the blood and clinical recovery in seven consecutive cases (six of which were streptococcal and one pneumococcal) treated with penicillin and heparin. These cases, however, had been observed only for short periods. One of the 10 cases reported by Kelson had received heparin and penicillin, supplemented toward the close of treatment by sulfadiazine.

On the basis of the data now available it is not possible to reach a definite conviction as to the efficacy of these measures, or as to what the best type of combined treatment may be. The favorable results reported by Kelson and White, and by Loewe, however, warrant further trial of these measures in clinics where large numbers of cases are available, and where the patients can be thoroughly studied and properly selected and the details of treatment adequately controlled. These procedures are still in the experimental stage, however, and until much more is known as to the results obtainable and the dangers involved, their promiscuous employment by those without experience is far more likely to do harm than good.

[4] KEEFER, C. S.: Discussion, Jr. Am. Med. Assoc., 1944, cxxi, 636.
[5] LOEWE, LEO, et al.: Combined penicillin and heparin therapy of subacute bacterial endocarditis, Jr. Am. Med. Assoc., 1944, cxxiv, 144–149.

REVIEWS

Chemistry and Physiology of the Vitamins. By H. R. ROSENBERG, Sc.D. 674 pages; 23.5 × 16 cm. Interscience Publishers, Inc., New York. 1942. Price, $12.00.

The author has made an outstanding contribution to the vitamin literature by presenting a comprehensive monograph on the chemistry and physiology of the vitamins. The introductory chapter includes a definition of the vitamins which distinguishes this group of substances from hormones and from various constituents of foods. Realizing certain limitations inherent in the definition, the author has justified its use and has suggested two new terms for substances which do not conform to the definition in all respects. Those enzymes which contain vitamins would be called vitazymes and those substances which act as sources of energy or as building units in addition to their vitamin-like functions would be termed vitagens. The latter group, including the essential fatty acids, essential carbohydrates, choline and related compounds, are discussed briefly in the appendix.

The vitamins are discussed according to their alphabetical nomenclature. The known information about each is systematically presented. All the names under which the vitamin has been known are listed, together with a chronological outline of the various discoveries which led to their chemical characterization of the vitamin. The historical survey is followed by a section on occurrence and distribution. The chemistry is thoroughly covered and includes isolation, properties, chemical constitution and synthesis, industrial methods of preparation, biogenesis, and methods of determination. Many of the chemical reactions are presented in detail. The methods for the determination of the vitamins are divided into chemical, biological, and biochemical. They are evaluated as to their accuracy, specificity and to their use in the determination of deficiency states. Other reactions useful for the detection of hypovitaminosis are also given. Various units which are in common use are compared with the international unit when possible.

The physiology of microörganisms, plants, and animals is given. The animal physiology is subdivided into the metabolism of the vitamin, the physiological basis for its action, together with a short review of the pathological aspects of hypovitaminosis.

Following the sections devoted to the known vitamins, the author has discussed briefly a group of the non-identified vitamins. These are substances which appear to be essential for the growth and development of certain animals or for bacteria, but further study is necessary to prove whether or not they are separate entities.

The book includes a list of abstracts of vitamin patents issued in the United States of America, Great Britain, Germany and France. These are arranged in the same general order as the rest of the text. There is a complete author and subject index.

The systematic presentation of the material, together with the extensive bibliography, makes this volume of great value to anyone interested in the vitamin field.

M. A. A.

BOOKS RECEIVED

Books received during November are acknowledged in the following section. As far as practicable, those of special interest will be selected for review later, but it is not possible to discuss all of them.

Savill's System of Clinical Medicine. Twelfth Edition. Edited by E. C. WARNER, M.D., F.R.C.P. 1168 pages; 22 × 15.5 cm. 1944. Williams and Wilkins Company, Baltimore. Price, $9.00.

Clinical Practice in Infectious Diseases. Second Edition. By E. H. R. HARRIES, M.D. Lond., F.R.C.P., D.P.H., and M. MITMAN, M.D. Lond., M.R.C.P., D.P.H., D.M.R.E. With a foreword by W. ALLEN DALEY, M.D. Lond., F.R.C.P., D.P.H. 570 pages; 22 × 15 cm. 1944. E. & S. Livingstone, Edinburgh. Price, $6.00.

The Art of Resuscitation. By PALUEL J. FLAGG, M.D. 453 pages; 23.5 × 16 cm. 1944. Reinhold Publishing Corporation, New York City. Price, $5.00.

Arthritis and Allied Conditions. Third Edition. By BERNARD I. COMROE, A.B., M.D., F.A.C.P. 1359 pages; 24 × 15.5 cm. 1944. Lea & Febiger, Philadelphia. Price, $12.00.

Bacteriology for Medical Students and Practitioners. Third Edition. By A. D. GARDNER, D. M., F.R.C.S. 264 pages; 17 × 11 cm. 1944. Oxford University Press, New York City. Price, $2.50.

An Outline of Tropical Medicine. By OTTO SAPHIR, M.D. 86 pages; 20 × 14 cm. 1944. The Michael Reese Research Foundation, Chicago.

Sulphonamides in the Treatment of Meningococcal Meningitis. Report to the Scientific Advisory Committee (Department of Health for Scotland). 20 pages; 24.5 × 15.5 cm. 1944. His Majesty's Stationery Office, Edinburgh. Price, $.10.

Escleroses Valvulares Calcificadas. Estudo Anátomo-Patológico, Radiológico e Clínico com Apresentação de cem Casos. By ROBERTO MENEZES DE OLIVEIRA, M.D. 154 pages; 23 × 16 cm. 1944. Tipografia do Patronato, Rio de Janeiro.

Arquivos da Polícia Civil de São Paulo. Volume VI (2.° Semestre)—1943; Volume VII (1.° Semestre)—1944. 468 pages (Vol. VI)—550 pages (Vol. VII); 28 × 19 cm. 1943 and 1944. Tip. do Gabinete de Investigações, São Paulo, Brasil.

COLLEGE NEWS NOTES

New Life Members

The College is gratified to announce that the following Fellows of the College became Life Members during the month of December:

Dr. Rudolph H. Sundberg, San Diego, Calif.
Dr. Frank J. Holroyd, Princeton, W. Va.
Dr. John H. Keating, New York, N. Y.

A.C.P. Members in the Armed Forces

Dr. Robert H. Siver (Associate), Cockeysville, Md., has entered upon active service as Captain, (MC), AUS, bringing the number of College members on active military duty to 1720.

The following members of the College have been honorably discharged from active duty:

Dr. Ellery G. Allen (Major, MC, AUS), Syracuse, N. Y.
Dr. A. Carlton Ernstene (Lt. Comdr., MC, USNR), Cleveland, Ohio

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Gifts to the College Library

Books

Dr. William Nimeh, F.A.C.P., Mexico, D. F.—"Alminar de la Medicina Arabe."
Dr. F. M. Pottenger, F.A.C.P., Monrovia, Calif.—"Symptoms of Visceral Disease," sixth edition.
Dr. James J. Waring, F.A.C.P., Denver, Colo.—"Quartercentenary of the Publication of Scientific Anatomy, 1543–1943." This book is dedicated to Dr. Waring and is No. 92 of a limited edition personally signed by the author, Nolie Mumey.

Reprints

Dr. Benjamin M. Bernstein, F.A.C.P., Brooklyn, N. Y.—1 reprint.
Daniel B. Faust, F.A.C.P., Colonel, (MC), AUS—1 reprint.
Jack D. Kirshbaum, (Associate), Lieutenant Colonel, (MC), AUS—1 reprint.
Dr. Louis Bonner Owens, F.A.C.P., Cincinnati, Ohio—1 reprint.
Frank B. Queen, F.A.C.P., Lieutenant Colonel, (MC), AUS—1 reprint.
James J. Waring, F.A.C.P., Denver, Colo.—4 reprints and a mimeographed monograph by the National Research Council, Division of Medical Sciences on, "Spontaneous Pneumothorax."

A.C.P. Regional Meeting at Chapel Hill, N. C.

A Regional Meeting of the College for the state of North Carolina was held at Chapel Hill November 3, 1944, under the general chairmanship of Dr. Paul F. Whitaker, F.A.C.P., Governor for North Carolina. The Program Committee consisted of Dr. William B. Dewar, F.A.C.P., Chairman, Dr. W. Reece Berryhill, F.A.C.P., and Dr. Thomas W. Baker, F.A.C.P. The program was conducted in the auditorium of the University of North Carolina School of Medicine. Presentations included: "Recent Advances in the Treatment of Cardiovascular Diseases," Dr. Ed-

ward S. Orgain (Associate), Durham; "The Value of X-Ray Examination as an Aid to the Diagnosis of Curable Heart Disease," Dr. James P. Rousseau, F.A.C.P., Winston-Salem; "Ageing," Dr. William DeB. MacNider, F.A.C.P., Chapel Hill; "Sarcoidosis," Dr. Paul P. McCain, F.A.C.P., Sanatorium; "A Consideration of Meckel's Diverticulum," Dr. Donnell B. Cobb, Goldsboro; "Chronic Non-calculous Cholecystitis," Dr. Claiborne T. Smith, F.A.C.P., Rocky Mount. In the evening a reception and dinner was given at the Carolina Inn, addressed by Dr. Whitaker, the Governor. About 100 physicians attended the meeting, of whom 60 (75% of the North Carolina members not on active military duty) were present.

The North Carolina state meeting of the College next year will be held at Duke University Medical School, Durham. Dr. James P. Rousseau, F.A.C.P., Dr. Edward S. Orgain (Associate), and Dr. E. M. Hedgpeth, F.A.C.P., constitute the new program committee.

A.C.P. Regional Meeting at Philadelphia

The 7th Annual Regional Meeting for Eastern Pennsylvania, New Jersey and Delaware was held at Philadelphia, December 15, 1944, in conjunction with the Postgraduate Course in Special Medicine, December 4–15, and the Annual Meetings of the Committees and Regents of the College. The program has previously been published in these columns. The scientific program, both morning and afternoon, was received with high acclaim. The evening Dinner Meeting was addressed by President Ernest E. Irons; Major General George F. Lull, Deputy Surgeon General, U. S. Army, Washington, D. C.; Brigadier General Charles R. Glenn, Deputy Air Surgeon, U. S. Army, Washington, D. C.; and Captain Richard Kern, (MC), USNR, envoy of the Surgeon General of the U. S. Navy.

The attendance from the Philadelphia area was extremely gratifying, since approximately 90% of local Fellows were present.

	Fellows	*Associates*	*Guests*	*Total*
(MC), U. S. Army	11	4	55	70
(MC), U. S. Navy	2		30	32
(MC), U. S. Public Health Service		1	2	3
	13	5	87	105
Civilians	148	25	100	273
Total Registration	161	30	187	378

The Haffenreffer Fellowship has been established at Brown University for the encouragement of advanced study and research under the direction of the Department of Medical Sciences.

It is open to graduates of approved medical schools, who have served an internship in an approved hospital, or who have had two or more years of practice. Training beyond a year of internship is a desirable qualification. Candidates for the fellowship must be persons of evident earnestness of purpose who have signified their intention of specializing in the field of internal medicine in practice, research or teaching.

The stipend is $1,800 per year; the duration, one year, with the expectation of a second year. Further information and applications may be obtained from the Department of Medical Sciences, Brown University, Providence, R. I.

Baruch Fellowships in Physical Medicine at Harvard

The Harvard Medical School announces Fellowships in Physical Medicine supported by grants from the Baruch Committee on Physical Medicine. The purpose of these fellowships is to provide a three year training for academic and clinical careers in the field of Physical Medicine. Fellowships are granted annually, but subject to renewal for a total duration of three years. The first year will be wholly or in part devoted to basic research related to Physical Medicine in one of the preclinical sciences such as physiology, anatomy or biophysics. The second year will be spent in clinical training in Physical Medicine at the Massachusetts General Hospital and other hospitals affiliated with the Harvard Medical School. In the third year fellows will be assistants in Physical Medicine with clinical responsibilities. For candidates with extensive previous training, one year clinical fellowships will also be granted.

Applicants must have an M.D. degree from an approved medical school and a minimum of one year internship in an approved hospital. The annual stipend will be $2500 (single), $3000 (married). Applications may be obtained from the Dean, Harvard Medical School, 25 Shattuck Street, Boston 15, Massachusetts.

The American Dietetic Association will hold its 28th Annual Meeting at the Netherland-Plaza Hotel, Cincinnati, Ohio, October 15–19, 1945.

Dr. Paullin Honored

Dr. James Edgar Paullin, F.A.C.P., was awarded the Certificate of Distinguished Achievement at appropriate exercises conducted by the Atlanta Chamber of Commerce at the Ansley Hotel, Atlanta, on Tuesday, November 21, 1944.

Col. Edgar V. Allen, (MC), AUS, Consultant in Medicine to the Seventh Service Command, is currently the Chairman of the Section on Experimental Medicine and Therapeutics of the American Medical Association.

Lt. Comdr. William L. Powers, (MC), USNR, (Associate), formerly of Wichita Falls, Texas, after twenty months in a hospital in the South Pacific, is now on duty with the U. S. Naval Hospital at Norman, Okla.

Lt. Col. Charles M. Caravati, (MC), AUS, F.A.C.P., has been transferred from the Percy Jones General Hospital, Battle Creek, Mich., to the Woodrow Wilson General Hospital, Staunton, Va., where he is Chief of Medical Service.

Dr. Carl R. Howson, F.A.C.P., has resigned as Medical Director of the La Vina Sanatorium and also as Medical Director of The Hastings Foundation for Tuberculosis Research of Pasadena, Calif., effective January 1, 1945, in order to devote himself entirely to private practice. The two positions are assumed on a full-time basis by Dr. Edward Kupka, F.A.C.P., recently Chief of the Bureau of Tuberculosis in the California Department of Public Health. The Hastings Foundation has purchased a plot of ground adjacent to the La Vina Sanatorium on which it is currently erecting the Charles Cook Hastings Home, which will house the research and sanatorium activities of the Foundation.

Dr. Samuel M. Feinberg, F.A.C.P., associate professor of medicine, Northwestern University Medical School, addressed the Academy of Medicine of Toledo, Ohio, November 10, on "Molds in Allergy—a Decade of Progress in the Etiology of Respiratory Allergy."

Lt. Col. J. W. H. Rouse, (MC), AUS, (Associate), formerly of San Antonio, Texas, is now commanding the 60th General Hospital in the Pacific area.

Lt. Comdr. Harold J. Harris, (MC), USNR, F.A.C.P., addressed the Graduate Fortnight of the New York Academy of Medicine, October 19, 1944 on "Brucellosis—Special Problems in Diagnosis and Treatment." Comdr. Harris addressed the Discussion Group of the Scientific Staff of The American Museum of Natural History on November 29, 1944 on "Animal Vectors in Brucella Infection."

Dr. Philip Reichert, F.A.C.P., Secretary of the New York Cardiological Society, 480 Park Ave., New York City, announces that the Society has inaugurated a project to study the rôle of trauma in the causation of cardiac disabilities. The work is planned as a continuing series of investigations and reports, with subcommittees on clinical statistics, on experimental investigation, on pathology, and on the medico-legal aspects. The general objective of the entire research is to study all angles of relationship between trauma and heart disease and to formulate, on the basis of the widest investigation possible, a reasonable code for the guidance of expert opinion. Funds for the work will be provided out of the Society's treasury and by various grants. An introductory meeting will take place January 24 at the New York Academy of Medicine. All interested organizations, practicing physicians and officials are invited to participate.

Col. John Minor, (MC), AUS, F.A.C.P., for nearly two years Chief of Medical Service at the Woodrow Wilson General Hospital, has been appointed Medical Consultant for the Third Service Command of the U. S. Army and is located at the Headquarters Third Service Command, Baltimore 2, Md.

Dr. Edward L. Turner, F.A.C.P., for many years President of the Meharry Medical College, Nashville, Tenn., resigned that appointment on January 1, 1945, to enter private practice in internal medicine at Bradford, Pa.

Michael Reese Hospital Offers Course in Electrocardiographic Interpretation

Dr. Louis N. Katz, F.A.C.P., Director of Cardiovascular Research at the Michael Reese Hospital, Chicago, announces that he will direct a course in electrocardiographic interpretation at that hospital from February 14 through May 2, 1945; the course to consist of twelve lectures, one a week on each Wednesday, from 7:00 to 9:00 p.m. The course is offered primarily to general practitioners in the Chicago area. The sessions will deal with the interpretation of electrocardiograms, illustrated by lantern slides. Emphasis will be placed on chest leads and on the importance of the electrocardiogram in coronary sclerosis and myocardial infarction. The mechanism and interpretation of heart irregularities will be developed. The fee for the course is $25.

Dr. William G. Leaman, Jr., F.A.C.P., Philadelphia, addressed the Eastern Section Meeting of the American Federation for Clinical Research at the Massachusetts General Hospital, Boston, December 9, 1944, on "The Prolonged Use of Mercupurin in Congestive Cardiac Failure."

REPORT FROM THE OFFICE OF THE SURGEON GENERAL, U. S. ARMY

Col. William C. Menninger, (MC), AUS, F.A.C.P., Chief Consultant in Neuropsychiatry, was the recipient of the first annual Lasker award in Mental Hygiene by the National Committee for Mental Hygiene at its New York annual meeting November 9. The award was given for "outstanding contribution to the mental health of the men and women of our Armed Forces."

Recent Promotions, Medical Corps Officers

Lieutenant Colonel to Colonel

Herman Lande, F.A.C.P., New York, N. Y.
Frank Dennette Adams, F.A.C.P., Brookline, Mass.
Neil Louis Crone, F.A.C.P., Boston, Mass.
Harold Foor Machlan, F.A.C.P., Hines, Ill.
Waldo Beattie Farnum, F.A.C.P., Riverdale, N. Y.

Major to Lieutenant Colonel

Robert Collier Page, F.A.C.P., Detroit, Mich.
Kendall Adams Elsom, F.A.C.P., Philadelphia, Pa.
Robert J. Needles, F.A.C.P., St. Petersburg, Fla.
James Porter Baker, F.A.C.P., Richmond, Va.
Andrew DeJ. Hart, Jr., F.A.C.P., Charlottesville, Va.
Frank Meyers, F.A.C.P., Buffalo, N. Y.
Joseph Bank, F.A.C.P., Phoenix, Ariz.
James Lewis Blanton, F.A.C.P., Fairmont, W. Va.
Ernest Marvin Tapp, (Associate), Walla Walla, Wash.
Philip Walling Brown, F.A.C.P., Rochester, Minn.
Milton Henry Clifford, F.A.C.P., Cambridge, Mass.
Dickinson Sergeant Pepper, F.A.C.P., Philadelphia, Pa.
Abraham Max Balter, F.A.C.P., Aspinwall, Pa.
William Walton Bondurant, Jr., F.A.C.P., San Antonio, Tex.
Hermon Camp Gordinier, (Associate), Troy, N. Y.

Lt. Col. Phillip T. Knies, F.A.C.P., Army Quarantine Liaison Officer, is directing a new quarantine branch in the Epidemiology Division, Preventive Medicine Service. The new program, which aims to extend precautionary measures throughout the Army's far-flung routes of travel, is part of the Medical Department's continuing battle against disease, which has given this country the healthiest fighting forces in the world and the healthiest soldiers in any war in history.

Major General George F. Lull, F.A.C.P., Deputy Surgeon General, dedicated the Vaughan General Hospital at Hines, Ill., recently. This hospital will specialize in medicine and psychiatry. Col. Victor C. Vaughan, in whose memory the hospital has been named, was one of the leading bacteriologists and toxicologists of his day. He was commissioned a Major in the U. S. Army during the Spanish War and was a member of the Commission headed by Walter Reed to study the cause and prevention of typhoid fever, then epidemic in military camps. During the World War, Colonel Vaughan served in the Office of The Surgeon General and was on

the executive committee of the general medical board of the Council of National Defense. He served as President of the American Medical Association and of the American Tuberculosis Association. He was awarded the Distinguished Service Medal for his outstanding work in epidemiology and was made a knight of the Legion of Honor by the French government. He died in 1929.

The Upjohn Company, Kalamazoo, Mich. was presented with the Army-Navy Award for their production record in supplying vital pharmaceuticals for the Armed Forces. In a letter to the Company Major General George F. Lull, F.A.C.P., Deputy Surgeon General, said, "The men and women of your Company can well be proud of your production record. Your organization has given this office the greatest cooperation in the supplying of pharmaceuticals—the use of which is vital and necessary in performing the mission of the medical department. The products you supply to the Medical Department have been outstanding both in volume produced and quality of production."

Brigadier General James S. Simmons, F.A.C.P., Chief of the Preventive Medicine Service, Surgeon General's Office, has been made President-Elect of the American Society of Tropical Medicine.

Brigadier General Hugh J. Morgan, F.A.C.P., Chief Consultant in Medicine, addressed the National Post-War Venereal Disease Conference held recently (Nov. 9 and 10) in St. Louis, Mo., on the "Treatment of Gonorrhea and Syphilis in the U. S. Army."

Dr. John Walker Moore, F.A.C.P., Louisville, Ky., has been made President-Elect of the Association of American Medical Colleges. Dr. William S. McEllroy, F.A.C.P., Pittsburgh, Pa, was elected Vice-President.

Dr. Virgil P. Sydenstricker, F.A.C.P., Professor of Medicine, University of Georgia School of Medicine, Augusta, has been commissioned Colonel, and will serve with the United Nations Relief and Rehabilitation Administration, as Chief Counsel in Nutrition of Western Europe.

Capt. Louis H. Roddis, (MC), USN, F.A.C.P., twice Editor of the Naval Medical Bulletin, will be responsible for the preparation of the Official Naval Medical History of the War. He will work at the Bureau of Medicine and Surgery, Washington.

Dr. Henry B. Mulholland, F.A.C.P., Charlottesville, was inducted as President of the Medical Society of Virginia at its last annual meeting in October.

Dr. William J. Bryan, F.A.C.P., Rockford, is now President of the Illinois Trudeau Society. Dr. David F. Loewen (Associate), Decatur, was chosen President-Elect.

Dr. E. K. Shelton, F.A.C.P., Los Angeles, recently received the honorary degree of Doctor of Science from the University of Colorado School of Medicine, Denver, from which he graduated in 1911.

Dr. Howard K. Petry, F.A.C.P., heretofore Medical Superintendent of the Harrisburg State Hospital, has recently been appointed Director of the Bureau of Mental Health of the Pennsylvania Department of Welfare.

Dr. Robin C. Buerki, F.A.C.P., Dean of the Graduate School of Medicine of the University of Pennsylvania, is now in Peru attending a hospital conference as a representative of the American Hospital Association.

Major Donald R. Ferguson, (MC), AUS, F.A.C.P., is now Chief of Medical Service, Regional Hospital, Camp McClellan, Ala., this appointment having been made on October 4, 1944.

Captain Gerald W. Smith, (MC), USN, F.A.C.P., formerly Commandant of the Philadelphia Naval Hospital, is now the Cammandant of Fleet Hospital No. 113, which was commissioned by the Navy on December 9. This hospital has a 2,000-bed capacity. In four months the entire hospital has been constructed—255 fifty-foot steel buildings, including Surgical, Medical and Neuro-psychiatric Wards; administration buildings; post office; laundry; galley and mess halls; operating room; laboratories, x-ray and dental departments; corpsmen's and nurses' quarters; garage, and maintenance buildings.

Colonel Robert E. Thomas, (MC), USA, F.A.C.P., Chief of the Hospitalization Division, United Kingdom Base, Communication Zone, European Theater of Operations, has been extended the honor of being elected a member of the Royal Society of Medicine of England.

A War Time Graduate Medical Meeting devoted to Hematology was held Dec. 7, 1944, at the Fletcher General Hospital, Cambridge, Ohio. The following program was presented. Greetings by Colonel Forrest R. Ostrander, M. C., Commanding. Dr. Bruce K. Wiseman, "The Leukopenic and Leukemic States—Their Differentiation and Therapy." Presentation of Cases from the Medical Service. Capt. Victor H. Kugel, M. C.—"Aplastic Anemia." Capt. Newell W. Howe, M. C.—"Purpura." Dr. Charles A. Doan, "The Anemic State—Its Recognition, Importance, Various Causes and Specific Treatment." Round Table Symposium, Major Arthur E. Rappoport, M. C., Presiding.

War-Time Graduate Medical Meetings

Region No. 3 (New York)—Dr. O. R. Jones, Chairman; Dr. N. Jolliffe, Dr. H. W. Cave.

Induction Center, Grand Central Palace, New York City, New York

January 19 Diagnosis and Treatment of Malaria—Dr. Henry E. Meleney
January 26 Diagnosis of Ano-rectal Disease—Dr. Max Cowett
(To be repeated on February 2)
February 9 Head Injuries—Dr. Eli Jefferson Browder
(To be repeated on February 16)

Region No. 4 (Eastern Pennsylvania, Delaware, New Jersey)—Dr. B. P. Widmann, Chairman; Dr. J. S. Rodman, Dr. S. P. Reimann.

U. S. Naval Hospital, Philadelphia, Pennsylvania

January 26 Common Mistakes in the Diagnosis and Treatment of Gastro-Intestinal Diseases—Dr. H. L. Bockus
February 9 Edema and Dehydration—Dr. F. William Sunderman
February 23 The Esophagus and Its Diseases—Dr. L. H. Clerf

REGION No. 5 (Maryland, District of Columbia, Virginia, West Virginia)—Dr. J. A. Lyon, Chairman; Dr. C. R. Edwards, Dr. C. B. Conklin.

Newton D. Baker General Hospital, Martinsburg, West Virginia

January 22 Protein Metabolism—Dr. John Scudder
February 5 Indications for Use of Sulfonamides and Penicillin—Dr. Henry B. Mulholland
The Psychoneuroses in War—Dr. David C. Wilson
February 19 Treatment of Patients with Paraplegia Due to War Injuries—Dr. Donald Munro
Liver Diseases Seen in the Present War—Dr. Wallace Yater.

A.A.F. Regional Hospital, Langley Field, Virginia

January 26 Chemotherapy—Dr. Henry B. Haag
Dermatology—Dr. Richard W. Fowlkes

U. S. Naval Hospital, Norfolk, Virginia

February 2 Nucleus Pulposus, Medical Aspect—Dr. Lay Martin
Nucleus Pulposus, Surgical Aspect—Dr. Francis J. Otenasek

REGION No. 8 (Western Pennsylvania, Ohio)—Dr. C. A. Doan, Chairman; Dr. P. G. Smith, Dr. F. M. Douglass.

Crile General Hospital, Cleveland, Ohio

January 23 Polycythemia—Dr. Russell H. Haden
February 27 Technique of Closure of Colostomies—Dr. Thomas E. Jones

Fletcher General Hospital, Cambridge, Ohio

January 18 Nutrition—Dr. Tom Spies
Diabetes—Dr. Cecil Striker

Air Base Hospital, Patterson Field, Dayton, Ohio

January 18 Therapy and Prevention of Rheumatic Fever—Lt. Commander Alvin Coburn, (MC), USNR
February 21 Diagnosis and Surgical Treatment of Acute Cholecystitis—Dr. George Heuer

Station Hospital, Lockebourne Air Base, Ohio

January 18 Psychosomatic Medicine—Dr. George T. Harding

REGION No. 14 (Indiana, Illinois, Wisconsin)—Dr. W. O. Thompson, Chairman; Dr. N. C. Gilbert, Dr. W. H. Cole, Dr. W. D. Gatch, Dr. R. M. Moore, Dr. H. M. Baker, Dr. E. R. Schmidt, Dr. E. L. Sevringhaus, Dr. F. D. Murphy.

Gardiner General Hospital, Chicago, Illinois

January 17 Conditions Affecting Glucose Metabolism
January 31 Brain and Spinal Cord Injuries

February 14 Diseases of the Intestinal Tract—Medical and Surgical Diagnosis and Care
February 28 Plexus and Peripheral Nerve Injuries

Station Hospital, Fort Sheridan, Illinois

January 17 Diseases of the Intestinal Tract—Medical and Surgical Diagnosis and Care
January 31 Plexus and Peripheral Nerve Injuries
February 14 Dermatological Diseases
February 28 Burns and Plastic Surgery

Mayo General Hospital, Galesburg, Illinois

January 17 Dermatological Diseases
January 31 Burns and Plastic Surgery
February 14 Malignancies in the Army Age Group—Medical X-Ray and Surgical Diagnosis and Treatment
February 28 Endocrinology

Vaughan General Hospital, Illinois

January 17 Malignancies in the Army Age Group—Medical X-Ray and Surgical Diagnosis and Treatment
January 31 Endocrinology
February 14 Virus and Rickettsial Diseases—Medical and Neurological Diseases and Treatment
February 28 Psychosomatic Medicine

Camp Ellis, Illinois

January 17 Virus and Rickettsial Diseases—Medical and Neurological Diseases and Treatment
January 31 Psychosomatic Medicine
February 14 Wound Healing and Tendon Surgery
February 28 Mental Hygiene and the Prevention of Neuroses in War

Chanute Field, Rantoul, Illinois

January 17 Repair of Bone in Fractures and Diseases
January 31 Arterial Vascular Disease—Traumatic Lesions
February 14 Blood Dyscrasias—Malaria—Filariasis
February 28 Diseases of the Kidneys—Uro-genital Tract

Truax Field, Wisconsin

January 17 Head and Spine Injuries—Dr. T. C. Erickson
January 31 Allergic States—Dr. Theodore L. Squier
February 14 Effects of Cold and Dampness, Frostbite—Colonel Irving S. Wright
February 28 Heart Disease—Dr. Chester M. Kurtz

REGION No. 16 (Missouri, Kansas, Arkansas, Oklahoma)—Dr. F. D. Dickson, Chairman; Dr. O. P. J. Falk, Dr. H. H. Turner.

Station Hospital, Rosecrans Field, St. Joseph, Missouri

February 15 Acute Respiratory Disease
Shock, Burns and Blood Derivatives

Regional Hospital, Fort Riley, Kansas

January 25	Clinical Psychiatry
	Neurology
February 15	Gastrointestinal Diseases
	X-ray Diagnosis

Station Hospital, Army Air Field, Great Bend, Kansas

January 18	Venereal Disease and Urology
	Anesthesia
February 8	Orthopedic Surgery
	Chemotherapy
	Physical Therapy

Winter General Hospital, Topeka, Kansas

January 18	Gastrointestinal Diseases—Dr. Carl R. Ferris
	General Surgery—Dr. Claude J. Hunt
February 22	Plastic and Maxillary Surgery—Dr. Earl C. Padgett
	Clinical Psychiatry—Dr. G. Leonard Harrington

The Portland Academy of Medicine held its annual dinner meeting at the Heathman Hotel on the evening of December 14, 1944.

The Academy was founded in 1906 for the purpose of aiding the Medical School Library and promoting desirable medical legislation in the State of Oregon. The Academy is made up of physicians and medical teachers in Portland and in Oregon. Total membership is 205. Of this group, 40 are in the Armed Forces. The functions of the Academy principally concern sponsoring three lectureships each year, presenting outstanding authorities in the various fields of medicine; aid to the University of Oregon Medical School Library; sponsoring of a Medical Research Foundation incorporated under the laws of the State of Oregon. This Foundation is organized to receive gifts for medical research and is administered by a committee made up of members of the Academy and prominent men of the State.

The program at the annual meeting consisted of an address by the president, Warren C. Hunter, M.D., Professor of Pathology at the University of Oregon Medical School. Dr. Hunter outlined the development of the Medical School during the years 1919 to 1924, a period during which the School experienced a most rapid growth and development. The guest of honor was Dr. Noble Wiley Jones, F.A.C.P., who has practiced Internal Medicine in Portland since 1906.

The following papers were presented in his honor: "His Contribution to Scientific Medicine," Dr. Laurence Selling, F.A.C.P., Professor of Medicine; "His Contribution to Practice of Medicine," Dr. Homer P. Rush, F.A.C.P., Associate Professor of Medicine; "His Contribution to Medical Education," Dr. Olaf Larsell, Professor of Anatomy.

During the past year the Academy has sponsored the following lectureships: March 9 and 10, "An Histological and Chemical Analysis of Precancerous Lesions" and "Factors in Ageing from Point of View of the Physician," Edmund V. Cowdry, Ph.D., Professor of Cytology, Washington University Medical School, Director of Research at Barnard Hospital Cancer Institute; May 18 and 19, "Criteria of Ovulation" and "The Sterility Problem," W. T. Pommerenke, Ph.D., M.D., Assistant Professor of Obstetrics and Gynecology, University of Rochester; October 11, "Malaria and Filariasis," L. T. Coggeshall, Comdr., (MC)–V(S), USNR, Marine Barracks, Klamath Falls, Oregon.

Plans for the coming year include lectures by Dr. Herbert F. Traut, Professor of Obstetrics and Gynecology at the University of California Medical School in San Francisco and by Dr. Joseph Erlanger, Emeritus Professor of Physiology at Washington University Medical School in St. Louis.

Dr. John Severy Hibben (Associate) was elected President of the Pasadena-Alhambra branch of the Los Angeles County Medical Society at its annual meeting on December 19.

Dr. Richard H. Freyberg, F.A.C.P., formerly Director of Arthritis and the Special Clinic for Rheumatic Disease at the University of Michigan Hospital, Ann Arbor, accepted an appointment as Director of the Department of Internal Medicine, Hospital for Special Surgery, on September 1, 1944, and has been located there since. He will be responsible for the activities of the medical division, both in-patient and out-patient medical clinic, and will be responsible for the development of the clinical laboratory. It is planned to develop also an excellent research laboratory with a broad research program.

A.C.P. Regional Meeting, Arkansas, Eastern Texas, Louisiana, Mississippi and Tennessee—Peabody Hotel, Memphis, January 25–26, 1945.

Program

Wm. C. Chaney, M.D., F.A.C.P.

General Chairman and Governor for Tennessee

Thursday, January 25, 1945

Morning Session

Presiding Officer

M. D. Levy, M.D., F.A.C.P.

Governor for Texas

9:00 Blood Plasma Protein Studies in Cardiac Edema.
George Herrmann, M.D., F.A.C.P., Galveston, Tex.

9:30 Underwater Physiotherapy as an Adjunct Measure in the Treatment of Impaired Function in Muscles and Joints. (Motion Picture.)
George Fletcher, M.D., F.A.C.P., Hot Springs National Park, Ark.

10:00 Bacterial Endocarditis. (Slides.)
Edgar Hull, M.D., F.A.C.P., New Orleans, La.

10:30 Neurasthenia.
T. S. Hill, M.D., (by invitation), Memphis, Tenn.

Symposium on Malaria

11:00 Introduction.
W. C. Colbert, M.D., F.A.C.P., Memphis, Tenn.
Master of Ceremonies
R. B. Watson, M.D., (by invitation), Memphis, Tenn.
Clinical Pathology of Malaria.
L. W. Diggs, M.D., (by invitation), Cleveland, Ohio.
Clinical Manifestations of Malaria.
Henry Packer, M.D., (by invitation), Memphis, Tenn.

Pathologic Physiology of Malaria.
HARRY FELDMAN, M.D., (by invitation), Captain, (MC), AUS, Memphis, Tenn.
Diagnosis and Treatment of Malaria.
FRANKLIN MURPHY, M.D., (by invitation), Lieutenant, (MC), AUS, Memphis, Tenn.

12:30 LUNCHEON.

AFTERNOON SESSION

Presiding Officer

O. C. MELSON, M.D., F.A.C.P.

Governor for Arkansas

2:00 Psychosomatic Concepts in Gastro-enterology.
CHARLES T. STONE, M.D., F.A.C.P., Galveston, Tex.

2:30 Planning Our Post-War Health Program.
FELIX J. UNDERWOOD, M.D., F.A.C.P., Jackson, Miss.

3:00 Retinal Changes in Vascular Diseases.
E. C. ELLETT, M.D., (by invitation), Memphis, Tenn.

3:30 Observations on Peptic Ulcer in the Army.
W. F. HOLLENBECK, M.D., F.A.C.P., Lieutenant Colonel, (MC), AUS, Memphis, Tenn.

4:00 Motion Picture on Malaria (from the Departments of Preventive Medicine and Anatomy, The University of Tennessee College of Medicine, Memphis).
T. S. ELIOT, Ph.D., (by invitation), Memphis, Tenn.

EVENING PROGRAM

HOTEL PEABODY

7:15 P.M.—Reception and Cocktails

8:00 P.M.—Banquet (Informal)

Toastmaster

O. W. HYMAN, Ph.D.

Dean, The University of Tennessee College of Medicine, Memphis

Address

ERNEST E. IRONS, M.D., F.A.C.P., President

American College of Physicians, Chicago, Ill.

Distinguished Guests

GEORGE C. THOMAS, Rear Admiral, U. S. Navy, Officer in Charge of the Professional Division, Bureau of Medicine and Surgery, Washington, D. C.

HUGH J. MORGAN, Brigadier General, U. S. Navy, Chief Consultant in Medicine, Washington, D. C.

LEROY E. BURNEY, Medical Director, U. S. Public Health Service, District No. 4, New Orleans, La.

WALTER BAUER, Colonel, U. S. Army, Consultant in Medicine, Eighth Service Command, Dallas, Tex.

James E. Paullin, Regent, Atlanta, Ga.
Charles T. Stone, Regent, Galveston, Tex.
C. W. Dowden, Chairman, Board of Governors, Louisville, Ky.
E. R. Loveland, Executive Secretary, Philadelphia, Pa.
L. W. Diggs, Cleveland, Ohio.
Russell L. Haden, Cleveland, Ohio.

Governors of the College:

John G. Archer, Greenville—Governor for Mississippi.
Wm. C. Chaney, Memphis—Governor for Tennessee.
Edgar Hull, New Orleans—Governor for Louisiana.
M. D. Levy, Houston—Governor for Texas.
O. C. Melson, Little Rock—Governor for Arkansas.

Friday, January 26, 1945

Morning Session

Presiding Officer

John G. Archer, M.D., F.A.C.P.

Governor for Mississippi

9:00 Chronic Constrictive Pericarditis: Report of Four Cases. (Lantern Slides.)
Charles Chamberlain, M.D., F.A.C.P., Fort Smith, Ark.

9:30 The Clinical and Roentgenographic Signs of Herniation of the Cervical Intervertebral Disc.
J. E. Whiteleather, M.D., (by invitation) Memphis, Tenn.

10:00 Histamine Headache.
C. W. Dowden, M.D., F.A.C.P., Louisville, Ky.

10:30 Significance of the Plasma Proteins.
L. A. Crandall, M.D., (by invitation), Memphis, Tenn.

Clinical Pathological Conference

11:00 Case Presentation.
W. C. Colbert, M.D., F.A.C.P., Memphis, Tenn.
Clinical Discussion.
Conley H. Sanford, M.D., F.A.C.P., Memphis, Tenn.
General Discussion.
Pathologic Findings.
Douglas H. Sprunt, M.D., (by invitation), Memphis, Tenn.

12:30 Luncheon.

Afternoon Session

Presiding Officer

Edgar Hull, M.D., F.A.C.P.

Governor for Louisiana

2:00 Observations on the Medical Program Sponsored by the Surgeon General of the United States Navy.
James E. Paullin, M.D., F.A.C.P., Atlanta, Ga.

3:00 The Treatment of Rheumatoid Arthritis.
RUSSELL L. HADEN, M.D., F.A.C.P., Cleveland, Ohio.

A.C.P. REGIONAL MEETING, OKLAHOMA CITY, February 23, 1945

Oklahoma, Kansas, Missouri, Western Texas, Nebraska

Lea A. Riely, M.D., F.A.C.P., General Chairman and Governor for Oklahoma

Tentative Program

On February 22, the Oklahoma City Internists Club will present its program. That evening the Regional Dinner Meeting of the College will be held at the Oklahoma Biltmore Hotel; brief addresses will be made by Dr. Ernest E. Irons, F.A.C.P., Chicago, President of the College, by Captain Willard J. Riddick, (MC), U.S.N., District Medical Officer of the Eighth Naval District, New Orleans, as official envoy of the Surgeon General of the Navy, by Colonel Edgar V. Allen, (MC), A.U.S., F.A.C.P., Consultant in Medicine of the Seventh Service Command of the Army, Omaha, as official envoy of the Surgeon General of the Army.

The scientific program for February 23 will be as follows: "Usual and Unusual Gastrointestinal Radiology," Dr. G. M. Tice of the University of Kansas; "Rheumatic Fever," Dr. Don Carlos Peete, of the University of Kansas; "Asthma," Dr. Harry Alexander, St. Louis; "Role of Calcium Metabolism in Circulatory Disease," Dr. Graham Asher, Kansas City; "Arthritis," Colonel Edgar V. Allen, Omaha; "Penicillin," Major Carl Dietrick, Borden General Hospital, Chickasha; "Some Observations on Thiouracil," Dr. Homer A. Ruprecht, Tulsa; "Acute and Chronic Local Ventricular Ischemia," Dr. R. G. Bayley, Oklahoma City; titles yet to be announced by Dr. Henry Turner, Oklahoma City, Dr. O. C. Melson, Little Rock, Dr. M. D. Levy, Houston, Capt. Willard J. Riddick, New Orleans, Col. Walter Bauer, Dallas, and Major General David N. W. Grant, Washington.

Coöperating with the Chairman are the College Governors for Kansas, Dr. Harold Jones; for Missouri, Dr. Ralph Kinsella; for Texas, Dr. M. D. Levy; for Nebraska, Dr. Warren Thompson.

At a meeting of the Board of Regents at Philadelphia, December 16, 1944, the following elections to membership in the College were made:

ELECTIONS TO ASSOCIATESHIP

Amtman, Leo, Chicago, Ill.
Appelman, Howard Benjamin, Detroit, Mich.
Ashe, William Francis, Jr., Cincinnati, Ohio, (MC), AUS
Atwater, John Spencer, Rochester, Minn., (MC), USNR
Autry, Daniel Hill, North Little Rock, Ark., (MC), AUS

Baldwin, Robert Sherman, Marshfield, Wis., (MC), AUS
Barnum, Glenn Lewis, Pasadena, Calif., (MC), USNR
Bean, William Bennett, Cincinnati, Ohio, (MC), AUS
Beard, Edmund Earl, Cleveland, Ohio
Bell, James Roeder, Cleveland, Ohio, (MC), AUS
Boehrer, John James, Minneapolis, Minn.
Boikan, William Sclair, Chicago, Ill.
Bortz, Donald Worcester, Cleveland, Ohio, (MC), USNR
Brannon, William Tappan, New Orleans, La.
Brewen, Stewart Ferdinand, Wormleysburg, Pa., (MC), AUS
Brownley, Harvey Christian, Lynchburg, Va., (MC), AUS
Brownstein, Samuel R., New York, N. Y., (MC), AUS

Cain, James Clarence, Rochester, Minn., (MC), AUS
Callaway, James Willis, La Jolla, Calif., (MC), AUS
Cecil, Richard Colbert, Richmond, Va.
Chapman, William Holmes, Jr., Suffolk, Va., (MC), AUS
Cheskin, Louis Joseph, Newark, N. J., (MC), AUS
Churukian, Giragos Missak, Paris, Ill.
Cogan, Michael Aaron, Holyoke, Mass., (MC), AUS
Cohen, Aaron, Brooklyn, N. Y.
Comanduras, Peter Diacoumis, Detroit, Mich.
Conway, William Hynes, New Rochelle, N. Y., (MC), AUS
Cook, Joseph Russell, Huntington, W. Va., (MC), AUS
Coombs, Frederick Stanley, Jr., Youngstown, Ohio, (MC), AUS

Darnall, Charles Milton, Austin, Tex., (MC), AUS
Davie, John Holmes, Philadelphia, Pa., (MC), AUS
Davis, Hal, Roanoke, Va., (MC), AUS
Day, Hughes Winfield, Kansas City, Kan.
Dolkart, Ralph Elson, Chicago, Ill.
Drake, Ellet Haller, Detroit, Mich., USPHS (R)
Dunham, Charles Little, Chicago, Ill., (MC), AUS
Durkin, John Keenan, Bryn Mawr, Pa., (MC), USNR

Erickson, Eldon Wesley, Detroit, Mich.
Ershler, Irving Leonard, Syracuse, N. Y.
Everett, Peter, III, New Orleans, La., (MC), AUS

Farmer, Charles Hall, Macon, Ga.
Feffer, James Joseph, Washington, D. C.
Fenichel, Nathan Milton, Brooklyn, N. Y.
Finkelstein, David, Philadelphia, Pa., (MC), AUS
Flynn, Joseph Eugene, Iowa City, Iowa, (MC), AUS
Friedland, Elmer, Buffalo, N. Y., (MC), AUS
Friedman, Maurice Harold, Chicago, Ill., (MC), AUS
Frisch, Robert Abraham, Milwaukee, Wis., (MC), AUS
Frist, Thomas Fearn, Nashville, Tenn., (MC), AUS
Fruchter, Harold, Long Island City, N. Y.

Geddis, James Thomas Joseph, New York, N. Y., (MC), AUS
Gelbach, Philip Delmont, Detroit, Mich.
Glenn, Paul Mitchell, Cleveland, Ohio, (MC), AUS
Glidden, Henry Spencer, Tewksbury, Mass., (MC), USNR
Goldstein, Milton Joseph, Scranton, Pa., (MC), AUS
Goldstein, Philip, New York, N. Y., (MC), AUS
Gray, Joel Boyd, New Orleans, La.
Gray, Seymour Jerome, Chicago, Ill.
Grier, George Smith, III, Newport News, Va., (MC), AUS
Grishaw, William Harry, Los Angeles, Calif., (MC), AUS

Harris, Hilbert Lawrence, Syracuse, N. Y.
Hassett, Florence Sullivan, Elmira, N. Y.
Herndon, James Henry, Dallas, Tex., (MC), AUS
Hiller, Glenn Ivan, Detroit, Mich.
Hinnant, Iredell Melvin, Cleveland, Ohio, (MC), AUS
Hoffman, Byron Jay, Atlanta, Ga., (MC), AUS
Holden, Lawrence Wheelock, Boulder, Colo.
Hollands, Robert Arthur, Pasadena, Calif., (MC), AUS
Humphrey, Arthur Allan, Battle Creek, Mich., (MC), USNR
Hurevitz, Hyman M., Davenport, Iowa, (MC), AUS

Israel, Harold Louis, Philadelphia, Pa., (MC), AUS

Johnson, V(esey) Marklyn, West Palm Beach, Fla.

Kammerer, William Henry, New York, N. Y., (MC), AUS
Kaplan, Bernard Irving, New York, N. Y., (MC), AUS
Kaplan, George, Woodside, L. I., N. Y., (MC), AUS
Kaufman, Benjamin, Brooklyn, N. Y.
Kavee, Julius, New York, N. Y.
Keinigsberg, Aaron, Chicago, Ill.
Killian, Dorothea Maria, Philadelphia, Pa.
Kinney, Robert John, Madison, Wis.
Kirsner, Joseph Barnett, Chicago, Ill., (MC), AUS
Kirstein, Melvin B., St. Louis, Mo., (MC), AUS
Klainer, Max Joseph, Stoneham, Mass., (MC), AUS
Klosk, Emanuel, Newark, N. J.
Knowlton, Richard Stanley, Cleveland, Ohio, (MC), AUS
Kopp, Israel, Boston, Mass., (MC), AUS
Kossmann, Charles Edward, New York, N. Y., (MC), AUS
Krainin, Philip, New York, N. Y., (MC), USNR
Krieger, Edward Myers, Wilmington, Del.

Learner, Norman, Philadelphia, Pa., (MC), AUS
Lee, Joseph Howard, Hamilton, Ont., Can.
Lefeber, Edward James, Galveston, Tex.
Levy, Charles, Wilmington, Del.
Levy, Joseph, New Rochelle, N. Y., (MC), AUS
Lieder, Louis Eugene, Cleveland, Ohio, (MC), AUS
Lief, Victor Filler, Far Rockaway, N. Y., (MC), AUS
Lindahl, Wallace William, Rochester, Minn., (MC), AUS
Lipton, Harry Robert, Atlanta, Ga., USPHS (R)
Litwins, Joseph, New York, N. Y., (MC), AUS
Lozner, Eugene Leonard, Boston, Mass., (MC), USNR
Lutz, Edgar Harvey, Montrose, Pa., (MC), AUS

Macdonald, Hugh, Glenview, Ill., (MC), AUS
Macdonald, William Charles, St. Louis, Mo.
MacNiel, Alec Cameron, Cleveland, Ohio, (MC), AUS
Madsen, H(enry) Vernon, Detroit, Mich.
McDaniel, Lewis Tillman, Boston, Mass., (MC), AUS
McLaughlin, James Alphonsus, Boston, Mass., (MC), USNR
McLochlin, Ralph Edwin, Little Rock, Ark., (MC), USNR
McNitt, Harry Arnold Hull, Washington, D. C.
Medoff, Joseph, Philadelphia, Pa., (MC), AUS
Menefee, Elijah Eugene, Jr., Durham, N. C.
Miller, John Fleek, Newark, Ohio, (MC), AUS
Mills, Charles Selby, Phoenix, Ariz., (MC), AUS
Moench, Louis Gardner, Salt Lake City, Utah
Moloney, William Curry, Boston, Mass., (MC), AUS
Monaco, Thomas Clifford, Boston, Mass., (MC), AUS
Moody, Rollen Wayne, Denver, Colo.
Myerson, Samuel, New York, N. Y., (MC), AUS
Myhre, William Norwood, Spokane, Wash., (MC), USNR

Norman, James Kindred, New Orleans, La., USPHS (R)

O'Connell, William Joseph, Jr., Detroit, Mich.
Offutt, Vernon Delmas, Kinston, N. C.
Olsen, Alonzo Young, Los Angeles, Calif., (MC), AUS

Page, Sidney Grey, Jr., Richmond, Va., (MC), AUS
Paull, Ross, La Jolla, Calif., (MC), AUS
Penner, Sidney Lincoln, Stratford, Conn., (MC), AUS
Pfeiffer, Mildred Clara Julia, Philadelphia, Pa.

Pignataro, Frank P., Marlboro, N. J., (MC), AUS
Porter, Reno Russell, Boston, Mass., (MC), AUS
Post, Joseph, New York, N. Y., (MC), AUS
Priddle, William Welmore, Toronto, Ont., Can., RCAMC

Randall, William Spears, Jr., Pensacola, Fla., (MC), AUS
Ranges, Hilmert Albert, New Rochelle, N. Y.
Ray, Edward Scott, Richmond, Va.
Raynolds, Arthur Hidden, New York, N. Y., (MC), AUS
Read, William Alexander, Cleveland, Ohio, (MC), AUS
Redish, Jules, Lynbrook, L. I., N. Y.
Roberts, Joseph Thomas, Washington, D. C.
Robertson, Alexander David, Willard, Ohio, (MC), AUS
Rosenberg, David Harry, Chicago, Ill., (MC), USNR
Rueger, Milton Jerome, Detroit, Mich., (MC), AUS

Sauer, William George, Rochester, Minn., (MC), AUS
Scheifley, Charles Holland, Rochester, Minn., (MC), AUS
Schmidt, Richard Hermann, Jr., Statesan, Wis.
Shillito, Frederick Hopkins, New York, N. Y.
Shuler, James Benjamin, Washington, D. C., (MC), U. S. Navy
Sittler, William Walter, Chicago, Ill., (MC), USNR
Smith, Richard Henry, Washington, D. C., USPHS
Spivey, Russell Jordan, Indianapolis, Ind., (MC), AUS
Spurr, Charles Lewis, Chicago, Ill.
Starrs, Robert Alphonsus, Ottawa, Ont., Can.
Steele, George Chapin, West Springfield, Mass.
Storey, William Edward, Columbus, Ga., (MC), AUS
Stuart, Byron McClellan, New Orleans, La.
Sullivan, William John, Bronxville, N. Y., (MC), USNR
Suter, James Marion, Bristol, Va., (MC), AUS
Sweigert, Charles Francis, San Francisco, Calif., (MC), AUS

Taylor, Robert Dewey, Indianapolis, Ind.
Townsend, Stuart Ross, Montreal, Que., Can.
Turner, Oliver Edmonds, Pittsburgh, Pa.
Tweddell, John Thomson, Kingston, Ont., Can.

Vance, William Clifford, Richmond, Ind., (MC), AUS
Van Ormer, William Alfred, Cumberland, Md., (MC), AUS

Walker, Douglass Willey, New Haven, Conn., (MC), AUS
Wallace, Joseph James, Washington, D. C., (MC), AUS
Waller, William Kennedy, Baltimore, Md., (MC), AUS
Waud, Sydney Peyster, Chicago, Ill., (MC), AUS
Weinstock, Samuel, Brooklyn, N. Y.
Wendkos, Martin Howard, Philadelphia, Pa., (MC), AUS
Wever, George Kuhn, Stockton, Calif., (MC), AUS
Whinnery, Randall Allen, Detroit, Mich.
White, Benjamin Vroom, Hartford, Conn., (MC), USNR
Whitehead, Duncan, Utica, N. Y., (MC), AUS
Wilcox, Charles Frederick, Ottawa, Ont., Can.
Williams, John Ralston, Jr., Winston-Salem, N. C.
Williams, Robert Hardin, Boston, Mass.
Winik, Irving Wolfe, Washington, D. C.

Winsor, Travis, New Orleans, La.
Wolfram, Julius, Dallas, Tex., (MC), AUS
Wood, William Hoge, Jr., Charlottesville, Va., (MC), AUS
Worsley, Thomas Luther, Jr., Baltimore, Md., (MC), AUS
Wosika, Paul Henry, Chicago, Ill.
Zavod, William Abraham, Mount Vernon, N. Y., (MC), AUS

ELECTIONS TO FELLOWSHIP

Abbott, Gordon Arthur, Washington, D. C., USPHS
Adlersberg, David, New York, N. Y.
Alden, Ruel Lawrence, Hempstead, N. Y., (MC), AUS
Allan, Warde Baunton, Baltimore, Md.
*Allen, Raymond Bernard, Chicago, Ill.
Altschul, Alexander, New York, N. Y.

Bagwell, John Spurgeon, Dallas, Tex., (MC), AUS
Barry, George Newton, Oklahoma City, Okla.
Bates, Robley Dunglison, Jr., Richmond, Va., (MC), AUS
Baxmeier, Robert Ivan, Pittsburgh, Pa.
Beckh, Walter, San Francisco, Calif.
Beeman, Carl Burritt, Grand Rapids, Mich., (MC), AUS
Bell, Robert A., Washington, D. C., (MC), U. S. Navy
Bellet, Samuel, Philadelphia, Pa.
Benson, Kenelm Winslow, Berkeley, Calif.
Blankfort, Gerald, Little Rock, Ark., (MC), AUS
Blumenthal, Jacob Solomon, Minneapolis, Minn.
*Boyer, Norman Howard, Boston, Mass., (MC), AUS
*Brown, Clarence Frank Gunsaulus, Chicago, Ill.
Brown, Madelaine Ray, Boston, Mass.
Brown, Robert Whitcomb, Fort Steilacoom, Wash.

Carroll, Hubert Henry, Washington, D. C., (MC), U. S. Navy
Chaikin, Nathan Wolf, New York, N. Y.
Charney, Louis Harry, Oklahoma City, Okla., (MC), AUS
Chasnoff, Julius, New York, N. Y., (MC), AUS
Chester, William, Mamaroneck, N. Y., (MC), AUS
Clifford, Milton Henry, Boston, Mass., (MC), AUS
Closson, James Harwood, Philadelphia, Pa., (MC), USNR
Coggin, Charles Benjamin, Los Angeles, Calif., (MC), AUS
Cook, Katharine Stewart, Troy, N. Y.
Crone, Neil Louis, Boston, Mass., (MC), AUS

*Dow, Robert Stone, Portland, Ore.
Drewyer, Glenn Edward, Flint, Mich., (MC), USNR
*DuBois, Franklin Smith, New Canaan, Conn.
Dugan, William Miller, Indianapolis, Ind.

Engbring, Gertrude Mary, Chicago, Ill.

Faison, Elias Samson, Charlotte, N. C.
Fidler, Roswell Schiedt, Columbus, Ohio
Finkelstein, William, Waterbury, Conn.
Fitts, Ralph Lamar, Grand Rapids, Mich., (MC), AUS
Flinn, Robert Harrold, Washington, D. C., USPHS
Freyberg, Richard Harold, New York, N. Y.
Friedlander, Richard Dufficy, San Francisco, Calif., (MC), AUS
*Friend, Dale Gilbert Forrestt, North Attleboro, Mass., (MC), AUS

Gibbons, Marion Noville, Cleveland, Ohio
*Gilbert, Newell Clark, Chicago, Ill.
Glenney, Wilton Ross, Pottsville, Pa., (MC), AUS
Grieco, Emil Henry, Bayonne, N. J., (MC), AUS

Harris, Alfred William, Dallas, Tex.
Harris, Fred William, Little Rock, Ark.
Hedgpeth, Edward McGowan, Chapel Hill, N. C.

Hiestand, Robert Forgy, Cincinnati, Ohio
Helm, Standiford, Evanston, Ill., (MC), AUS
*Howard, Marion Edith, New Haven, Conn.
Howell, Llewelyn Pennant, Rochester, Minn.
*Huber, Harry Lee, Chicago, Ill.
*Jacobs, Henry Russell, Evanston, Ill.
Kenamore, Bruce Delozier, St. Louis, Mo., (MC), AUS
Kirk, Robert Chester, Columbus, Ohio, (MC), AUS
Klein, Andrew John Valois, Orange, N. J., (MC), AUS
Kleinbart, Morris, Philadelphia, Pa.
Kroon, Harry Charles, Syracuse, N. Y., (MC), AUS

Lancaster, William Ewart Gladstone, Fargo, N. D.
Lang, Frederick Robert, Washington, D. C., (MC), U. S. Navy
Leach, John Edward, Paterson, N. J., (MC), AUS
Lemere, Frederick, Seattle, Wash., (MC), AUS
*Levine, Philip, Newark, N. J.
Logue, Robert Bruce, Atlanta, Ga., (MC), AUS
Lowe, Robert Chester, New Orleans, La.
Lyons, Richard Hugh, Ann Arbor, Mich.

Mackie, George Carlyle, Wake Forest, N. C.
Manchester, Benjamin, Washington, D. C.
Mass, Max, Macon, Ga.
*McKinlay, Chauncey Angus, Minneapolis, Minn.
*Miller, C(harles) Phillip, Chicago, Ill.
Montgomery, Hugh, Philadelphia, Pa., (MC), USNR
Mooney, James Ivan, Rochester, N. Y.
Morehead, Robert Page, Winston-Salem, N. C.
Morgan, William Palmer, Austin, Tex.
*Mugrage, Edward Rosseter, Denver, Colo.
Murray, Norman Lovell, Summit, N. J., (MC), AUS
*Nadler, Walter Herman, Chicago, Ill.
Neiman, Benjamin Harold, Oak Park, Ill., (MC), AUS
Nesbitt, Samuel, New Haven, Conn., (MC), USNR

Parent, Sol(omon) S., Newark, N. J., (MC), AUS
Patmos, Martin, Kalamazoo, Mich., (MC), AUS
Pierson, Daniel Brown, Jr., Philadelphia, Pa.
*Popper, Hans Philipp, Chicago, Ill.
Pruitt, Francis Willard, Washington, D. C., (MC), U. S. Army

Rauschkolb, John Edward, Cleveland, Ohio
Ravid, Jacob Mordecai, Brooklyn, N. Y.
Reich, Carl, New York, N. Y.
*Reimann, Hobart Ansteth, Philadelphia, Pa.
Ricen, Edgar, Washington, D. C., (MC), U. S. Navy
Roberts, Ella, Philadelphia, Pa.
Robishaw, Ruth Alice, Cleveland, Ohio
Rosenthal, Phillip Jacob, Pittsburgh, Pa.
Rowland, E(ly) Driver, Hot Springs National Park, Ark., (MC), AUS

Sacks, Milton Samuel, Baltimore, Md.
Schnur, Sidney, Houston, Tex., (MC), AUS
Scholder, Bernard Morris, Mt. Vernon, N. Y., (MC), USNR
Schoolnic, Jacob Wolfe, East Liverpool, Ohio
Schroeder, Henry Alfred, New York, N. Y., (MC), USNR
*Sheaff, Howard Martin, Oak Park, Ill.
Slowey, James Francis, Cleveland, Ohio
Smith, Henry Leon, Detroit, Mich.
Sohval, Arthur Robert, New York, N. Y.
Souders, Carlton Remsberg, Boston, Mass., (MC), AUS
Sprague, Randall George, Rochester, Minn.
*Stead, Eugene Anson, Jr., Decatur, Ga.
Stebbins, Henry Dows, Marblehead, Mass.

Stefanic, Edward Joseph, Lakewood, Ohio
Steigmann, Frederick, Chicago, Ill., (MC), USNR
Strawbridge, Rendall Risley, Philadelphia, Pa.
Stubenbord, William Dorus, New York, N. Y., (MC), USNR
*Sweetser, Horatio Bartholomew, Jr., Minneapolis, Minn., (MC), USNR

*Tice, James Winfred, Hamilton, Ont., Can., RCAF
Toone, Elam Cooksey, Jr., Richmond, Va., (MC), AUS
Trenis, John Watkins, Washington, D. C., (MC), AUS

* Direct to Fellowship

*Vorhaus, Martin Grossman, New York, N. Y.

Walter, Henry, Jr., Lancaster, Pa.
Ware, Robert Lane, Washington, D. C., (MC), U. S. Navy
Warren, Harry Allen, Champaign, Ill., (MC), AUS
Williams, Lawrence Arthur, Pasadena, Calif.
Willis, Willard Harlan, Utica, N. Y., (MC), AUS
*Winkler, Alexander Woodward, New Haven, Conn.

Zillhardt, Jacob Charles, Binghamton, N. Y.
Zimmerman, Frederick Thomas, New York, N. Y.

OBITUARIES

DR. PHILIP FOSTER BARBOUR

Dr. Philip Foster Barbour, M.D., F.A.C.P.: Born, Danville, Ky., February 24, 1867; A.B. (1884), A.M. (1900), Central University of Kentucky; M.D., 1890, Hospital College of Medicine, now the University of Louisville; for many years, Clinical Professor, Diseases of Children, and head of the department, University of Louisville School of Medicine; from 1898 to 1908, Professor of Pediatrics, Hospital College of Medicine; Diplomate, American Board of Pediatrics; member and State Chairman, American Academy of Pediatrics; President, Kentucky State Medical Association, 1932; former President, Kentucky State Pediatric Society and Louisville Society for Mental Hygiene; Medical Chairman, Kentucky White House Conference; member, Association of American Teachers of Diseases of Children and Southern Medical Association; Fellow of the American Medical Association and American College of Physicians (the latter since 1920); Consulting Pediatrician, Kentucky State Department of Health and Kentucky State Baptist Orphan Asylum; formerly, Visiting Pediatrician, Louisville City Hospital; formerly, Consultant in Pediatrics, Kosair Crippled Children Hospital; Consulting Pediatrician and formerly Chief of Staff, Children's Free Hospital; Trustee, Centre College; died in St. Anthony's Hospital November 1, 1944, age, 77.

Dr. Barbour was often referred to as the Dean of Southern Pediatrics and has probably trained more men in this specialty than any other individual in the South. Dr. Barbour was extremely active throughout his

entire life and the last few years of his practice were devoted almost entirely to the care of indigent children. His erect youthful figure was often seen on the golf courses where he usually humbled his younger opponents with a score in the 70's. Dignified, God-fearing, scholarly, and friendly to his conferees and patients alike, he will be greatly missed in the entire Southland.

C. W. Dowden, M.D., F.A.C.P.,
Governor for Kentucky

DR. JAMES PATRICK JORDAN

Dr. James Patrick Jordan (Associate), North Tonawanda, N. Y., died July 23, 1944, of bronchopneumonia at the age of 44.

Dr. Jordan was born on December 5, 1899. He received his Bachelor of Science degree at Canisius College in 1922, and his medical degree from the St. Louis University School of Medicine in 1932. After an internship of one year at the Sisters' Hospital, he spent two additional years as a Resident in the Millard Fillmore Hospital of Buffalo, and remained on the staff of that hospital for many years, having been Attending Physician at the time of his death.

Dr. Jordan was a Diplomate of the National Board of Medical Examiners; he did postgraduate work at Cook County Hospital, Chicago, and the Peter Bent Brigham Hospital, Boston. He entered the Medical Corps of the U. S. Naval Reserve on October 26, 1942, as Lieutenant Commander, and his death occurred in the South Atlantic Area, off the coast of South America.

Dr. Jordan was a very conscientious and enthusiastic worker and had gone a long way in his professional career. His passing is a great loss to Buffalo.

Nelson G. Russell, Sr., M.D., F.A.C.P.,
Governor for Western New York

DR. FREDERICK CASPER RINKER

Dr. Frederick Casper Rinker of Norfolk, Virginia, died on November 15, 1943. Dr. Rinker was born in Upperville, Virginia, on May 30, 1885. His academic education was acquired at Roanoke College, Virginia, where he received his Bachelor of Arts degree in 1906. In 1911 he graduated from the Department of Medicine of the University of Virginia and shortly became Resident Physician at the Philadelphia Polyclinic Hospital, where he remained for a year. Later, he became Assistant Physician at the Pennsylvania Hospital for Nervous and Mental Diseases, Philadelphia, remaining through 1912. The University of Wisconsin Medical School then claimed his services as instructor in Clinical Medicine, 1913–1914, Assistant Professor of Clinical Medicine, 1915–1919.

In the last named year, Dr. Rinker moved to Norfolk, Virginia, where he remained until the time of his death. Dr. Rinker was one of Norfolk's prominent physicians, a member of the Staff of the Norfolk Protestant Hospital, the Lee Memorial Hospital, and the Norfolk General Hospital. As Former Treasurer of the Seaboard Medical Association, Past President of the Southside Medical Association, Member of the Norfolk County Medical Society, Virginia State Medical Society, American Medical Association, Fellow of the American College of Physicians since 1922, and a Diplomate, American Board of Internal Medicine, he fully proved his true interest in the field of Internal Medicine.

During the first World War, Dr. Rinker was a First Lieutenant in the R.O.T.C., University of Wisconsin (Contract Surgeon). In 1935, he was appointed Lieutenant Commander in the U. S. Naval Reserve.

Dr. Rinker always displayed a keen and lively interest in the problems of Internal Medicine. He was active in the medical society of his state and always had a bright and cheering word, tinctured with pertinent observation. His death seems particularly untimely owing to the fact that his energy and enthusiasm had changed so little with the advancing years. His friends will miss him. His wife, two brothers and a sister survive.

J. Edwin Wood, Jr., M.D., F.A.C.P.,
Governor for Virginia

DR. ROBERT LENOX BARNES

Dr. Robert Lenox Barnes, an Associate of the American College of Physicians, was born in Washington, C. H., Ohio, May 19, 1886, and died at his residence, 1337 Bryden Road, Columbus, Ohio, on August 3, 1944. Dr. Barnes graduated from the College of Medicine of the Ohio State University in 1910. Soon after his graduation he became a member of the teaching staff of his Alma Mater, and for a time was an instructor of Clinical Pathology. His practise was limited to Internal Medicine paying particular attention to diseases of the cardio-vascular system, and to the treatment of arthritis.

He was Chief of Staff of Mt. Carmel Hospital, with which institution he had been connected since his graduation. In addition to being an Associate of the College he was a member of the Columbus Academy of Medicine, Ohio State Medical Association, American Medical Association, American Heart Association and the American Society for the Study of Arthritis.

Dr. Barnes was a student, and in this country took post-graduate work at Harvard University, Johns Hopkins University and New York Post-Graduate School of Medicine. He spent the years 1930 to 1932 at the University of Vienna, Austria. He made a special study of arthritis in London in 1934 and in 1936.

He was a member of the Nu Sigma Nu Medical Fraternity, a 32nd degree Mason and a Methodist. He was an active member of the Columbus Club and the Scioto Country Club.

Dr. Barnes was admired and held in high esteem by his colleagues, and because of his personal interest in his patients he endeared himself in their hearts. He will be greatly missed. His widow and a sister survive.

CHARLES W. MCGAVRAN, M.D., F.A.C.P,.
Columbus, Ohio

DR. A. COMINGO GRIFFITH

With the death of Dr. A. Comingo Griffith on November 9, 1944, the American College of Physicians lost a fine friend, and his many friends and associates in Kansas City, Missouri, a fine doctor.

A. COMINGO GRIFFITH, M.D., F.A.C.P., Kansas City, Mo.
Former Governor and former Vice President, American College of Physicians

Dr. Griffith's influence extended far. After a preliminary education at Lawrenceville School and Princeton University, he obtained his degree in Medicine in 1906 at the University of Kansas. He added to this education much postgraduate work and entered a career in the practice of medicine well equipped to care for the sick. His interests led him into the best medical associations, local and national.

He became a Fellow of the American College of Physicians in 1922, and was a member of its Board of Governors from 1929 to 1942, and Third Vice-President 1942–1943. He helped to organize the Kansas City Southwest Clinical Society, was its President in 1936, and always worked for the success of its programs. He could be counted on to support every worthwhile medical project in his home city and elsewhere. He was a Diplomate of the American Board of Internal Medicine, a member of Jackson County Medical Society, Missouri State Medical Association, American Medical Association, and the Kansas City Academy of Medicine. He was most actively associated with St. Joseph Hospital.

Besides these public associations, there are the countless unrecorded associations carried in the affections of his friends and patients.

RALPH KINSELLA, M.D., F.A.C.P.,
Governor for Missouri

DR. OSCAR MONROE GILBERT

Dr. Oscar Monroe Gilbert, F.A.C.P., one of the outstanding internists of Colorado, died suddenly October 18, 1944, at his home in Boulder. Dr. Gilbert was born February 12, 1873, in Fulton, Missouri. In 1898 he graduated from the Barnes Medical College of St. Louis. His keen interest in keeping up with the advances of scientific medicine was reflected by frequent graduate work in such places as Johns Hopkins, Vienna, London and Munich, and his desire to impart scientific knowledge, by the fact that he was a member of the Faculty of the University of Colorado School of Medicine for thirty-four years. He was made Professor of Medicine, Emeritus, in that institution in 1934.

During his forty-four years as a resident of Boulder he found time for much activity in civic affairs. His professional activities were largely limited to the specialty of tuberculosis. He was President of the Colorado State Medical Society in 1913 and 1914. He served as a captain in World War I, and he is to be honored for his part in World War II for, in 1942, because of the shortage of civilian physicians, he returned to an active practice from which he had retired for many years.

In addition to his activities in County and State medical organizations and his Fellowship in the American College of Physicians, Dr. Gilbert was a Fellow of the American Medical Association and a member of the Denver Clinical and Pathological Society.

Besides his wife, Dr. Gilbert is survived by five children, three daughters and two sons, both of whom are physicians serving in the Armed Forces of the United States.

WARD DARLEY, M.D., F.A.C.P.,
Governor for Colorado.

DR. EDWARD LUTHER WHITNEY, F.A.C.P.

Dr. Edward Luther Whitney of Walla Walla, Washington, was born in Chatham, Medina County, Ohio, in 1870. His general education was in the public schools of Chatham; he later attended Oberlin College. He graduated in medicine at Baltimore Medical College (now part of the University of Maryland) and received the degree of Doctor of Medicine in April, 1895. He was then appointed assistant resident physician and surgeon at the college hospital. After one year, he became resident pathologist for the Maryland General Hospital, serving there from 1896 to 1901. During this period, he was instructor in pathology in Baltimore Medical College, continuing until 1916, the year he came west. He first settled in Portland, Oregon, and engaged in general practice, but in January, 1918, he moved to Walla Walla, Washington, beginning a professional career that was marked for its distinction and success.

Throughout his residence in Walla Walla, Dr. Whitney specialized in diagnosis and internal medicine, establishing an enviable reputation in this part of the State. He became a Fellow of the American College of Physicians in 1923. He was a Fellow of the American Medical Association; a member of the Washington State Medical Association, the Walla Walla County Medical Society (Past President), the American Chemical Society, and a Diplomate of the American Board of Internal Medicine.

When the war came, Dr. Whitney had attained the age at which many men would have sought retirement, or at least a sharp reduction in the number of his responsibilities. Like a good soldier, however, he continued his practice, and until stricken with the illness that cost his life, he ministered to the ill. He died on September 13, 1944, in Walla Walla of cerebral hemorrhage, and his loss will be keenly felt.

E. G. Bannick, M.D., F.A.C.P.,
Acting Governor for Washington